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FINAL YEAR B. PHARM.

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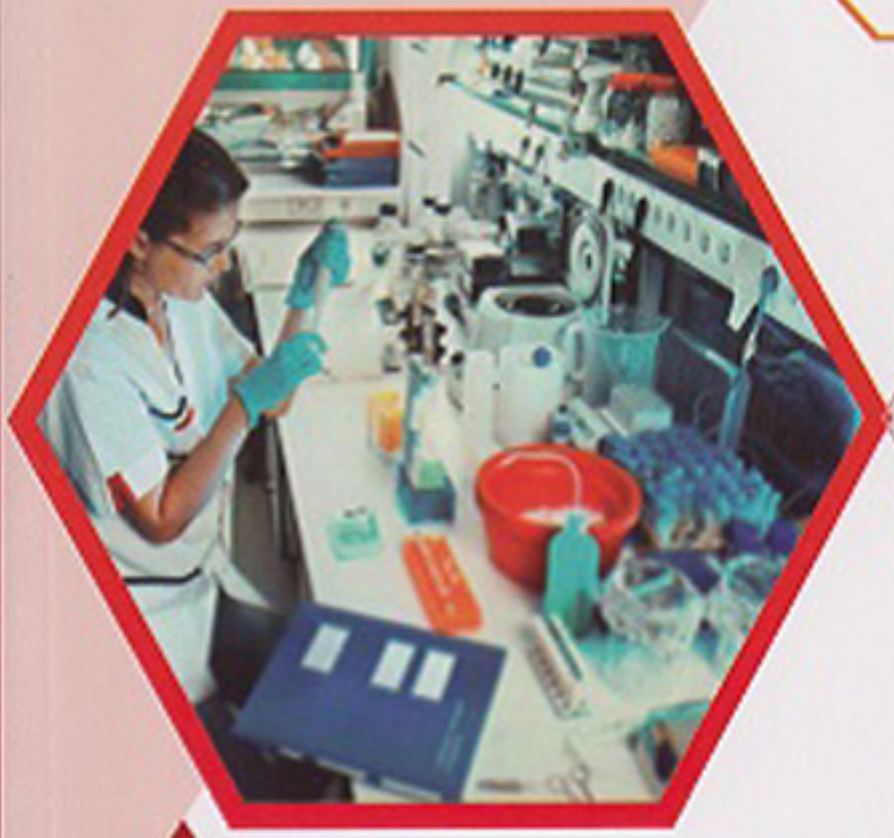

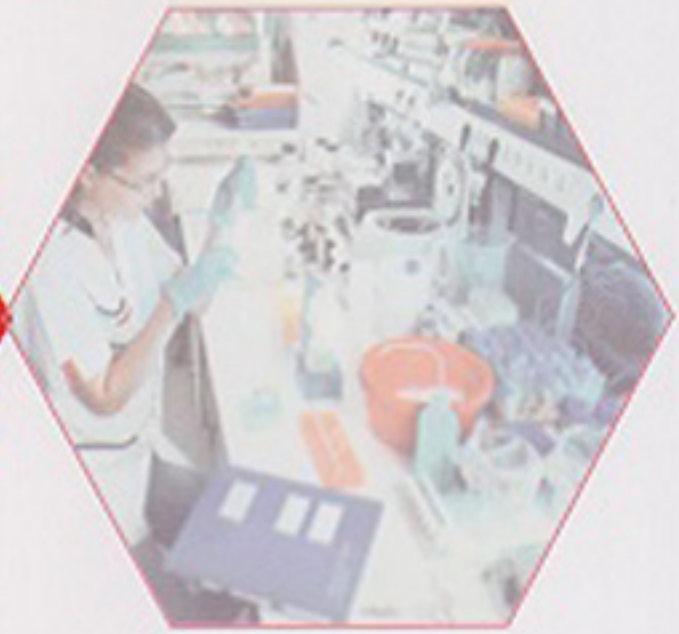

INDUSTRIAL PHARMACY-II

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NIRALI PRAKASHAN
ADVANCE MOUNT OF KNOWLEDGE

A Text Book of

INDUSTRIAL PHARMACY - II

As Per PCI Regulations

FINAL YEAR B. PHARM.

Semester - VII

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Preface

Industrial Pharmacy is the branch of Pharmacy that deals with scientific and technological aspects related to design and development of dosage forms. Pharmaceutical industry is made of hundreds of firms involved in discovery, development, production, and selling of drug products that meet regulatory requirements. The current curriculum implemented by Pharmacy Council of India, New Delhi as Regulation 2014 has Industrial Pharmacy-II subject at Semester-VII of final year of the B. Pharm. course.

This theory book covers whole of the topics specified in the syllabus. The book has been divided into five main chapters covering all the aspects related to Pharma Industry which include Pilot Plant Scale-up Techniques, WHO guidelines for Technology Transfer and various regulatory requirements for Drug Approval. All these chapters have been designed in very easy language, to the point coverage of all the topics, in pictorial/graphical manner so that every student can easily understand. After completion of this course students will able to understand Dosage forms and their Manufacturing Techniques and all the related and practical aspects of dosage form development. This also helps the students to correlate the theoretical knowledge with professional and practical need of Pharmaceutical industry.

Taking this as an opportunity, we have tried our level best to give detail insight of the subject expectations with respect to various regularity procedures followed for the final drug approval and WHO guidelines for transfer of technology. This book is first of its kind that it covers huge data on manufacturing techniques of various dosage forms. The course is beneficial for teachers, students and the industry personals. Efforts have been taken to elaborate basic concepts of pharmaceutical manufacturing and are supported with flow diagrams, figures, equations and data tables.

At the end of each Module a Review Questions which include MCQs, short answer questions and long answer questions are given that well help the students to assess the knowledge gained after reading all the modules.

Our sincere thanks are to **Shri Dineshbhai Furia** and **Shri Jignesh Furia** of **Nirali Prakashan, Pune,** for their co-operation and interest taken in publishing this book. We are also thankful to the staff of Nirali Prakashan, especially Roshan Khan, Mrs. Varsha Bodake, Mr. Malik Shaikh and Mr. Ravindra Walodare of Nirali Prakashan for bringing out this nicely printed book.

Authors

Syllabus

BP 702 T. INDUSTRIAL PHARMACY-II (Theory) (45 Hours)

UNIT-I (10 Hours)

Pilot Plant Scale-up Techniques: General considerations - including significance of personnel requirements, Space requirements, Raw materials, Pilot plant scale-up considerations for solids, liquid orals, semi solids and Relevant documentation, SUPAC guidelines, Introduction to platform technology.

UNIT-II (10 Hours)

Technology Development and Transfer: WHO guidelines for Technology Transfer (TT): Terminology, Technology transfer protocol, Quality risk management, Transfer from R & D to production (Process, packaging and cleaning), Granularity of TT Process (API, excipients, finished products, packaging materials) Documentation, Premises and equipments, Qualification and validation, Quality control, Analytical method transfer, Approved regulatory bodies and agencies, Commercialization - practical aspects and problems (case studies), TT agencies in India - APCTD, NRDC, TIFAC, BCIL, TBSE / SIDBI; TT related documentation - Confidentiality agreement, Licensing, MoUs, Legal issues.

UNIT-III (10 Hours)

Regulatory Affairs: Introduction, Historical overview of regulatory affairs, Regulatory authorities, Role of regulatory affairs department, Responsibility of regulatory affairs professionals.

Regulatory Requirements for Drug Approval: Drug development teams, Non-clinical drug development, Pharmacology, Drug metabolism and Toxicology, General considerations of Investigational New Drug (IND) Application, Investigator's Brochure (IB) and New Drug Application (NDA), Clinical research / BE studies, Clinical research protocols, Biostatistics in pharmaceutical product development, Data presentation for FDA submissions, Management of clinical studies.

UNIT-IV (08 Hours)

Quality Management Systems: Quality management and Certifications: Concept of quality, Total quality management, Quality by Design (QbD), Six-sigma concept, Out of Specifications (OOS), Change control, Introduction to ISO 9000 series of quality systems standards, ISO 14000, NABL, GLP.

UNIT-V (07 Hours)

Indian Regulatory Requirements: Central Drug Standard Control Organization (CDSCO) and State Licensing Authority: Organization, Responsibilities, Certificate of Pharmaceutical Product (CoPP), Regulatory requirements and approval procedures for new drugs.

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Contents

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Chapter ... 1

PILOT PLANT SCALE-UP TECHNIQUES

♦ LEARNING OBJECTIVES ♦

After completing this chapter, students will be able to understand:

- ❖ It is a part of the pharmaceutical industry where a lab scale formula is transformed into a viable product by the development of liable practical procedure for manufacture.
- ❖ Bench studies (Product characterization purity).
- ❖ Animal studies (toxicology, Pharmacokinetics PME, efficiency).
- ❖ Clinical Studies.
- ❖ Increasing compliance with regulations as product moves through testing and exaction.
- ❖ Increasing knowledge about the product.
- ❖ Increasing knowledge about the possible problems, snags, pitfalls with manufacture processing, packing, storing and installing the product.
- ❖ Ultimately facilitation of the transfer of product from laboratory into production.

1.1 INTRODUCTION

Pilot plant scale-up techniques involve reproducible manufacture of an experimental formulation on high-speed production equipment, in a cost-effective manner. It is a part of the pharmaceutical industry, where the same processes used during Research and Development (R & D) of dosage forms are applied to different output volumes; usually greater than that obtained during R & D.

In every emerging pharmaceutical industry or an already existing one, there is always a need to have an intermediate batch scale representing procedures and simulating that used for commercial manufacturing. It is achieved by determining the ability of formula to withstand batch scale and process modification.

There is equally a need for equipment evaluation and validation to ensure that the aim of your company which is the mass production of the drug in question is not defeated. For a pilot scale-up to be successful, a product must be capable of being processed in a large scale

often with equipment that only remotely resembles that used in the development laboratory. The idea is that you understand what makes these processes are similar, identify and eliminate many scale-up problems before investing large sum of money on a production unit.

Maintain the chemical attributes of the product, its quality and efficacy even though the production processes are modified as a result of sample size increase and equipment changes.

Pilot Plant Scale-up must include:

1. A close examination of the formula to determine its ability to withstand large scale and process modification.
2. A review of a range of relevant processing equipment to determine which would be most compatible with the formulation as well as the most economical, simple and reliable in producing the product.

During pilot plant scale-up ensure the:

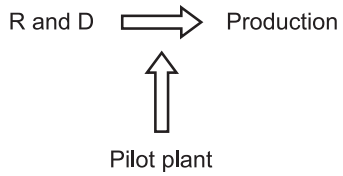
1. Determination of the availability of raw materials that consistently meet the specifications required to produce the product.
2. Determination of the physical space required and the layout of related functions to provide short-term and long-term efficiency.
3. Evaluation, validation and finalizing of production and process controls.
4. Issuing of adequate records and reports to support Good Manufacturing Practices (GMPs) and provision of the historical development of the production formulation process, equipment train and specifications.
5. Development and validation of meaningful product reprocessing procedures.
6. Identification of all critical, features of a scale up process, so that it can be adequately monitored to provide assurance that the process is under control and that the process at each level of the scale up maintains the specified attributes originally intended.
7. Production rate and future market requirements.

1.2 GENERAL CONSIDERATIONS DURING PILOT PLANT SCALE-UP

Pilot plant scale-up is of practical interest to formulation scientist/ production managers and should be considered from the inception of a development project. This is because a process using the same type of equipment can perform quite differently when the size of the equipment and the amount of material involved is significantly increased. The chemical attributes of the product, its quality and efficacy should be maintained even though the production processes modified as a result of sample size increase and equipment changes. You should also bear in mind that pilot plant scale-up, in itself, does not guarantee a smooth transition. A well-defined process may fail quality assurance tests in full manufacturing scale even after generating a perfect product in both the laboratory and the pilot plant.

Plant: It is place were the 5M's like Money, Material, Man, Method and Machine are brought together for the manufacturing of the products.

Pilot Plant: It is the part of the Pharmaceutical Industry where a lab scale fortune is transferred into a viable product by development of liable and practical procedure of manufacture.



Scale-up: It is the art for designing of prototype using the data obtained from the pilot plant model.

Objectives of Scale-up:

1. To try the process on a model of proposed plant before committing large sum of money on product unit.
2. To examine of the formula for determination of the ability to withstand batch scale.
3. Evaluation and validation for process and equipments.
4. To identify the critical features of the process.
5. To provide guidelines for production and process controls.
6. To provide master manufacturing formula with instruction for manufacturing produces.
7. To avoid the scale-up problems.

Steps in Scale-up:

Define product economics based on projected market size and competitive selling and provide guidance for allowable manufacturing cost.

↓

Conduct Laboratory studies and scale up planning at the same time.

↓

Define key ratter controlling steps in the proposed process.

↓

Conduct Preliminary larger-than laboratory studies with equipment to be used in rate controlling step in aid in plant design.

↓

Design and contract a pilot plant including provisions for process and environment controls, cleaning and sanitizing systems, packaging and waste handling systems, and meeting regulatory agency requirements.

↓

Evaluate pilot plants result (Product and process) including process economics to make any corrections and a decision on whether to process or not with a full-scale plant development.

1.3 NEED OF PILOT PLANT STUDIES

1. A pilot plant allows investigation of a product and process on an intermediate scale before large amount of money is committed to full scale production.
2. It is usually not possible to predict-the effects of a many-fold increase in scale.
3. It is not possible to design a large-scale processing plant from laboratory data alone with any degree of success.

❖ **A pilot plant can be used for:**

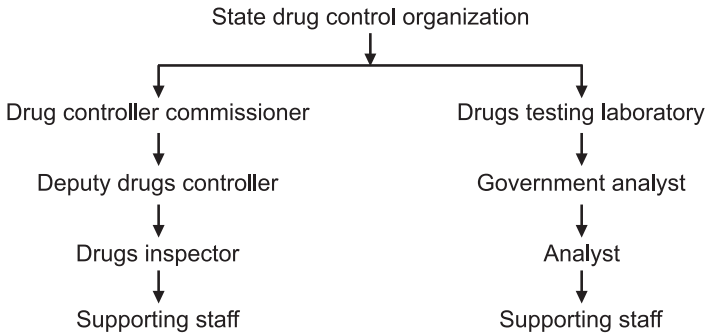
1. Evaluating the results of laboratory studies and making product of process.
2. Monitoring of quality of Drugs and Cosmetics, manufactured by respective state units and those marketed in the state.
3. Investigation and prosecution in respect of contravention of large provisions.
4. Administrative actions.
5. Pre and post licensing inspection.
6. Recall of sub-standard drugs state drug control organization.

1.4 STATE DRUG CONTROL ORGANIZATION

CDSCO joined with state drug control board organization to regulate the import/export of drugs and medical device.

The State Drug Control Organization is responsible for:

- Providing license to drug testing laboratories.
- Approving drug formulation for manufacture.
- Carrying out pre and post licensing.
- Observing the drug manufacturing process by respective state unit and those marketed in the state.



Functions of State Licensing Authorities:

1. Licensing of manufacturing site for drugs including API and finished formulation.
2. Licensing of establishment for sale or distribution of drugs.
3. Approval of drug testing laboratories.
4. Monitoring of quality of drugs and cosmetics marketed in the country.
5. Investigation and prosecution of contravention of legal provision.
6. Recall of sub-standard drugs.

1.5 USES OF PILOT PLANT

1. To evaluate the results of laboratory studies.
2. To make process corrections and improvements.
3. To produce small quantities of product for sensory, chemical, microbiological evaluations, limited market testing or furnishing samples to potential customers, shelf-live and storage stability studies.
4. To provide data that can be used in making a decision on whether or not to proceed to a full-scale production process; and in the case of a positive decision, designing and constructing a full-size plant or modifying an existing plant.

1.6 GENERAL REQUIREMENTS FOR PILOT SCALE AND SCALE-UP

1. Reporting Responsibilities:

(i) R and D group with separate staffing.

(ii) The formulator who developed the product can take into the production and provide support even after transition into production has been completed.

2. Personal Requirements:

(i) Scientists with experience in pilot plant operations as well as in actual production area are the most preferable, as they have to understand the intent of the formulator as well as understand the perspective of the production personnel.

(ii) The group should have some personnel with engineering knowledge as well as scale up also involves engineering principles.

3. Space Requirements:

(i) Administration and information process: Adequate office and desk space should be provided for both scientists and technicians. The space should be adjacent to the working area.

(ii) Physical testing area: This area should provide permanent bench top space for routinely used physical testing equipment.

(iii) Standard pilot-plant equipment floor space: Discrete pilot plant space, where the equipments are needed for manufacturing all types of dosage forms, is located.

(a) Intermediate sized and full-scale production equipment is essential in evaluating the effects of scale-up of research formulations and processes.

(b) Equipments used should be made portable. So that after use it can be stored in the small store room.

(c) Space for cleaning of the equipment should also be provided.

(iv) Storage area:

(a) It should have two areas divided as approved and unapproved area for active ingredients as well as excipients.

(b) Different areas should be provided for the storage of the in-process materials, finished bulk products from the pilot-plant and materials from the experimental scale-up batches made in the production. Storage area for the packing material should also be provided.

4. Review of the Formula:

(i) A thorough review of each aspect of formulation is important.

(ii) The purpose of each ingredient and its contribution to the final product manufactured on the small-scale laboratory and equipment should be understood.

(iii) Then the effect of scale-up using equipment that may subject the product to stresses of different types and degrees can more readily to be predicted, or recognized.

5. Raw Materials:

(i) One purpose/responsibility of the pilot plant is the approval and validation of the active ingredients and excipients raw materials.

(ii) Raw materials used in the small-scale production cannot necessarily be the representative for the large-scale production.

6. Equipments:

(i) The most economical and the simplest and efficient equipments, which are capable of producing product within the proposed specifications, are used.

(ii) The size of the equipments should be such that the experimental trial's run should be relevant to the production sized batches.

(iii) If equipment is too small, the process developed will not scale up; whereas if equipment is too big, then there is wastage of the expensive active ingredients.

7. Production Rates:

The immediate as well as the future market trends/requirements are considered while determining the production rates.

8. Process Evaluation Parameters:

(i) Order of mixing of components.

(ii) Mixing speed.

(iii) Mixing time.

(iv) Rate of addition of granulating agents, solvents, solutions of drug, etc.

(v) Heating and cooling rates.

(vi) Filters size (liquids).

(vii) Screen size (solids).

(viii) Drying temperature and drying time.

The knowledge of the effects of various process parameters as few mentioned above form the basis for process optimization and validation.

9. Master Manufacturing Procedures:

(i) The weight sheet should clearly identify the chemicals required in a batch. To prevent confusion the names and identifying numbers for the ingredients should be used on batch records.

(ii) The process directions should be precise and explicit.

(iii) A manufacturing procedure should be written by the actual operator.

Various specifications like addition rates, mixing time, mixing speed, heating, and cooling rates, temperature, storing of the finished product samples, etc. should be mentioned in the batch record directions.

10. Product Stability and Uniformity:

(i) The primary objective of the pilot plant is the physical as well as chemical stability of the products.

(ii) Hence each pilot batch representing the final formulation and manufacturing procedure should be studied for stability.

(iii) Stability studies should be carried out in finished packages as well as raw material.

1.7 GMP CONSIDERATIONS

1. Equipment qualification.
2. Process validation.
3. Regularly schedule preventative maintenance.
4. Regularly process review and revalidation.
5. Relevant written standard operating procedures.
6. The use of competent technically qualified personnel.
7. Adequate provision for training of personnel.
8. A well-defined technology transfer system.
9. Validated cleaning procedures.
10. An orderly arrangement of equipment so as to ease material flow and prevent cross-contamination.

❖ **Advantages:**

1. Members of the production and quality control divisions can readily observe scale-up runs.
2. Supplies of excipients and drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division.
3. Access to engineering department personnel is provided for equipment installation, maintenance and repair.

❖ **Disadvantages:**

1. The frequency of direct interaction of the formulator with the production personnel in the manufacturing area will be reduced.
2. Any problem in manufacturing will be directed towards its own pilot-plant personnel.

1.8 SCALE-UP

It is the art for designing of prototype using the data obtained from the pilot plant model.

Objectives:

1. **Formulation related**: Identification and control of critical components and another variable.
2. **Equipments related:** Identification and control of critical parameters and operating range.
3. **Production and process related:** Evaluation, validation and finalization of controls.
4. **Product related:** Development and validation of reprocessing procedures.
5. **Documentation:** Records and reports according to C-GMP.

Need of Scale-Up:

1. A well-defined process.
2. A perfect product in laboratory and pilot plant.
3. But may fail in QA tests.
4. Because processes are scale dependent.
5. Processes have differently on a small scale and a large scale.
6. Scale up is necessary to determine the effect of scale on product quality.

1.9 PILOT PLANT DESIGN FOR TABLETS

The primary responsibility of the pilot plant staff is to ensure that the newly formulated tablets developed by product development personnel will prove to be efficiently, economically and consistently reproducible on a production scale. The design and construction of the pharmaceutical pilot plant for tablet development should incorporate features necessary to facilitate maintenance and cleanliness. If possible, it should be located on the ground floor to expedite the delivery and shipment of supplies.

1. Formulation and process development.
2. Technology evaluation, scale-up and transfer.
3. Clinical supply manufacture.

Control Pilot Plant Studies:

1. A pilot plant allows investigation of a product and process on an intermediate scale before large amounts of money are committed to full-scale production.
2. It is usually not possible to predict the effects of a many-fold increase in scale.
3. It is not possible to design a large-scale processing plant from laboratory data alone with any degree of success.

Product Considerations:

1. Material Handling:

In the laboratory, materials are simply scooped or poured by hand, but in intermediate or large-scale operations, handling of these materials often become necessary. If a system is used to transfer materials for more than one product, steps must be taken to prevent cross

contamination. Any material handling system must deliver the accurate amount of the ingredient to the destination. More sophisticated methods of handling materials are vacuum loading systems, metering pumps, screw feed system.

2. Dry Blending:

Dry blend should take place in granulation vessel. Larger batch may be dry blended and then subdivided into multiple sections for granulation. All ingredients should be free of lumps, otherwise it causes flow problems. Screening and/or milling of the ingredients prior to blending usually makes the process more reliable and reproducible. The equipments used for blending are: V-blender, Double cone blender, Ribbon blender, Slant cone blender, Bin blender, Orbiting screw blenders, Vertical and horizontal high intensity mixers, etc.

Scale-up Considerations;

- Powders to be used for encapsulation or to be granulated prior to tableting must be well blended to ensure good drug distribution.
- Inadequate blending could result in drug content uniformity variation, especially when the tablet or capsule is small and the drug concentration is relatively low.
- Ingredients should be lumps free, otherwise it could cause flow problems.

3. Granulations:

The most common reasons given to justify granulating are: to impart good flow properties to the material, to increase the apparent density of the powders, to change the particle size distribution, uniform dispersion of active ingredient, etc. Traditionally, wet granulation has been carried out using, sigma blade mixer, heavy-duty planetary mixer:

- to improve the flow properties.
- to increase the apparent density of the powder.
- to change the particle size distribution so that the binding properties on compaction can be improved.

Direct compression method: A small amount of potent active ingredient can be dispersed most effectively in a carrier granulation, when the drug is dissolved in granulating solution and added during the granulating process.

Wet granulation has been carried out by using:

- Sigma blades.
- Heavy-duty planetary mixture.
- High speed chopper blades used in mixing of light powders.
- Multifunctional processors, dry blending, wet granulation, drying, sizing and lubricating.
- Effect of binding agent.

4. Drying:

The most common conventional method of drying a granulation continues to be the circulating hot air oven, which is heated by either steam or electricity. The important factor to consider as part of scale up of an oven drying operation are airflow, air temperature, and the depth of the granulation on the trays.

Fluidized Bed Dryer:

- Optimum loads - rate of airflow.
- Inlet air temperature.
- Humidity.
- Data used for small scale batches (1-5 kg) cannot be extrapolate processing conditions for intermediated scale (100 kg) or large batches.

5. Reduction in Particle Size:

- Particle size to particle size distribution is important to the compression characteristics of a granulation.
- Compression factors may be affected by the particle size distribution, flow ability, compressibility, uniformity of tablet weight, content uniformity, tablet hardness, tablet colour uniformity.

Equipments:

- Oscillating granulator
- A hammer mill.
- Screening device.

Too large particle size causes:

- Weight variation
- Mottling

Too fine particle size causes:

- Weight variation.
- Capping.
- Both oversized and undersized granulation can adversely affect tablet content uniformity.
- Lubricants and Giants are added at final blend.

6. Blending:

- The attention should be paid to scale-up of the right design is used and blender loads, mixing speeds, mixing timing are properly established.
- In any blending operation segregation and mixing occurs simultaneously, both processes are function of a particle size, shape, hardness, density and dynamics of the mixing action.
- Low dose active ingredients are directly compressed.

Equipments:

- Planetary type mixer
- Twin shell mixture
- Cone type

Over loading in blender:

- Retards the free flow of granules
- Reduces the efficiency
- Causes content un-uniformity

If the load is to small:

- Powder blend slides rather than roll in blender.
- It causes improper mixing.

7. Slugging:

A dry powder blend cannot be directly compressed because of poor flow or compression properties. This is done on a tablet press designed for slugging, which operates at pressures of about 15 tons, compared with a normal tablet press, which operates at pressure of 4 tons or less. Slugs range in diameter from 1 inch, for the more easily slugged material, to ¾ inch in diameter for materials that are more difficult to compress and require more pressure per unit area to yield satisfactory compacts. If an excessive amount of fine powder is generated during the milling operation, the material must be screened and finely recycled through the slugging operation.

8. Compression:

The ultimate test of the tablet formulation and granulation can be compressed on a high-speed tablet press.

Steps involved during compression:

(i) Filling empty die cavity with granulation.
(ii) Pre-compression of granules.
(iii) Compression of granules.
(iv) Ejection of tablet from the die cavity.

Compression characteristics can be evaluated by press speed equal to normal production speed.

Then detect the problems such as,

- Sticking to punch surface
- Tablet hardness
- Capping
- Weight variation

Granules must be delivered at adequate rate.

9. Tablet Coating:

❖ **Pan and fluidized coating:**

- Optimum tablet load.
- Operating tablet bed temperature.

- Drying airflow rate and temperature.
- The solution application rate.
- The size and shape of the nozzle aperture (for airless sprayer).
- The atomizing air pressure and the liquid flow rate (for air atomized sprayers).

❖ **Pan coating:**

- Fixed operating parameters.
- Variable operating parameters.
- Other parameters; Pan Loading (kg), Solid content of coating suspension (% w/w), Spray gun dynamics, Drying Air (cfm), Inlet air temperature (°C), Gun to tablet bed distance, Coating System Spray rate (g min^{-1}), Quantity of coating applied (% w/w), Atomizing air pressure (psi, bar), Air Pressure (psi, bar), Pan speed Number of spray guns.

❖ **Fluidized bed coating:**

- Batch size.
- Drying/fluidizing air volumes.
- Spray nozzle dynamics.
- Spray evaporation rate.

Equipments:

- Conventional coating pan.
- Perforated pans of fluidized-bed coating column.

Types:

- Sugar coating.
- Film coating.

(i) Tablet must be sufficiently hard to withstand the tumbling to which they are subjected while coating.

(ii) Operation conditions to be established for pan or column operation are optimum tablet load, operating tablet, bed temperature, drying air flow rate, temperature, solution application rate.

1.10 PILOT PLANT SCALE-UP TECHNIQUES FOR CAPSULES

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft soluble container or shell of a suitable form of gelatin.

Different Steps in capsule production:

1. Mixing of ingredients
2. Granulation and lubrication
3. Making of capsules
4. Filling of capsules
5. Uniformity testing
6. Packing and labeling

Both tablets and capsules are produced from ingredients that may be either dry blended or wet granulated to produce a dry powder or granule mix with uniformly dispersed active ingredients. To produce capsules on high speed equipment, the powder blend must have the uniform particle size distribution, bulk density and compressibility required to promote good flow properties and result in the formation of compact of the right size and sufficient cohesiveness to be filled into capsule shells.

1.10.1 Manufacturing of Hard Gelatin Capsules

Shell Composition:

- **Gelatin:** It is prepared by the hydrolysis of collagen. There are two basic types of gelatin: Type-A and Type-B. The two types can be differentiated by their isoelectric points (7.0 - 9.0 for type-A and 4.8 - 5.0 for type-B) and by their viscosity and film forming characteristics.

  Combination of pork skin and bone gelatin is often used to optimize shell characteristics. The physicochemical properties of gelatin of most interest to shell manufactures are the bloom strength and viscosity.
- **Colorants:** Various soluble synthetic dyes (coal tar dyes) and insoluble pigments are used. Colorants not only play a role in identifying the product, but also play a role in improving patient compliance. For example, white - analgesia, lavender - hallucinogenic effects, orange or yellow - stimulants and antidepressants.
- **Opaquing agents:** Titanium dioxide may be included to render the shell opaque. Opaque capsules may be employed to provide protection against light or to conceal the contents.
- **Preservatives:** When preservatives are employed, parabens are often selected.

Shell Manufacturing:

- **Dipping:** Pairs of the stainless-steel pins are dipped into the dipping solution to simultaneously form the caps and bodies. The pins are at ambient temperature; whereas the dipping solution is maintained at a temperature of about 50^{o}C in a heated, jacketed dipping pan. The length of time to cast the film has been reported to be about 12 sec.
- **Rotation:** After dipping, pins are elevated and rotated 2-1/2 times until they are facing upward. This rotation helps to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends.
- **Drying:** The racks of gelatin coated pins are then passed into a series of four drying ovens. Drying is mainly done by dehumidification. A temperature elevation to only a less degrees is permissible to prevent film melting. Under drying will leave the films too sticky for subsequent operation.
- **Stripping:** A series of bronze jaws strip the cap and body portions of the capsules from the pins.

- **Trimming:** The stripped cap and body portions are delivered to collects in which they are firmly held. As the collects rotate, knives are brought against the shells to trim them to the required length.
- **Joining:** The cap and body portions are aligned concentrically in channels and the two portions are slowly pushed together.
- **Sorting:** The moisture content of the capsules as they are from the machine will be in the range of 15-18% w/w. During sorting, the capsules passing on a lighted moving conveyor are examined visually by inspectors. Defects are generally classified according to their nature and potential to cause problems in use.
- **Printing:** In general, capsules are printed before filling. Generally, printing is done on offset rotary presses having throughput capabilities as high as three-quarter million capsules per hour.
- **Sizes and Shapes:** For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 to 5.

  The largest size normally acceptable to patient is a No. 0. Three larger sizes are available for veterinary use: 10, 11, and 12 having capacities of about 30, 15, and 7.5 gm, respectively. The standard shape of capsules is traditional, symmetrical bullet shape. Some manufactures have employed distinctive shapes. For example, Lilly's pulvule tapers to a bluntly pointed end, Smith Kline Beacham's spansule capsules taper at both the cap and body ends.
- **Sealing:** Capsules are sealed and somewhat reshaped in the Etaseal process. This thermal welding process forms an indented ring around the waist of the capsule where the cap overlaps the body.
- **Storage:** Finished capsules normally contain an equilibrium moisture content of 13-16% to maintain a relative humidity of 40-60% when handling and storing capsules.

Filling of Hard Gelatin Capsules:

- Equipments used in capsule filling operations involve one often of two types of filling systems:
  (i) **Zanasi or Martelli encapsulator:** Forms slugs in a dosatar which is a hollow tube with a plunger to eject capsule plug.
  (ii) **Hofliger-Karg machine:** Forms compacts in a die plate using tamping pins to form a compact.
- In both these systems, the scale-up process involves bulk density, powder flow, compressibility and lubricant distribution. Overly lubricated granules are responsible for delaying capsule disintegration and dissolution.
- Osaka Model R-180 Semi-Automatic Capsule Filling Machine.

1.10.2 Manufacturing of Soft Gelatin Capsules

Composition of the shell:

- Similar to hard gelatin shells, the basic component of soft gelatin shell is gelatin; however, the shell has been plasticized.
- The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and can vary from 0.3-1.0 for very hard shell to 1.0-1.8 for very soft shell.
- Upto 5% sugar may be included to give a "chewable" quality to the shell.
- The residual shell moisture content of finished capsules will be in the range of 6-10%.

Formulation:

- Formulation for soft gelatin capsules involves liquid, rather than powder technology. Materials are generally formulated to produce the smallest possible capsule consistent with maximum stability, therapeutic effectiveness and manufacture efficiency. The liquids are limited to those that do not have an adverse effect on gelatin walls. The pH of the lipid can be between 2.5 and 7.5. Emulsion cannot be filled because water released from it will affect the shell.
- The types of vehicles used in soft gelatin capsules fall into two main groups:
  (i) Water immiscible, volatile or more likely more volatile liquids such as vegetable oils, mineral oils, medium-chain triglycerides and acetylated glycerides.
  (ii) Water miscible, non-volatile liquids such as low molecular weight PEG has come into use more recently because of their ability to mix with water readily and accelerate dissolution of dissolved or suspended drugs. All liquids used for filling must flow by gravity at a temperature of 35°C or less. The sealing temperature of gelatin films is 37°C - 40°C.

Manufacture Processes:

1. **Plate Process:** The process involves:
   - Placing the upper half of a plasticized gelatin sheet over a die plate containing numerous die pockets,
   - Application of vacuum to draw the sheet into the die pockets,
   - Filling the pockets with liquor or paste,
   - Folding the lower half of gelatin sheet back over the filled pockets, and
   - Inserting the "sandwich" under a die press where the capsules are formed and cut out.
2. **Rotary Die Press:**
   - In this process, the die cavities are machined into the outer surface of the two rollers.
   - The die pockets on the left-hand roller form the left side of the capsule and the die pockets on the right-hand roller form the right side of the capsule.

- Two plasticized gelatin ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism.
- As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules.

3. Accogel Process:

- In general, this is another rotary process involving a measuring roll, a die roll, and a sealing roll.
- As the measuring roll and die roll rotate, the measured doses are transferred to the gelatin-linked pockets of the die roll.
- The continued rotation of the filled die converges with the rotating sealing roll where a second gelatin sheet is applied to form the other half of the capsule. Pressure developed between the die roll and sealing roll seals and cuts out the capsules.

4. Bubble Method:

- The Globex Mark II capsulator produces truly seamless, one-piece soft gelatin capsules by a "bubble method". A concentric tube dispenser simultaneously discharges the molten gelatin from the outer annulus and the liquid content from the tube. By means of a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets that consist of a liquid medicament core within a molten gelatin envelop. The droplets assume a spherical shape under surface tension forces and the gelatin congeals on cooling. The finished capsules must be degreased and dried.

1.10.3 Soft/Liquid-filled Hard Gelatin Capsules

- Three formulation strategies based on having a high resting viscosity after filling have been described:
  - Thixotropic formulations,
  - Thermal-setting formulations,
  - Mixed Thermal-Thixotropic systems.

  The more the lipophilic contents, the slower is the release rate. Thus, by selecting excipients with varying HLB balance, varying release rate may be achieved.
- To produce capsules on high-speed equipment, the powder blend must have,
  - Uniform particle size distribution.
  - Bulk density.
  - Formation of compact of the right size and of sufficient cohesiveness to be filled into capsule shells.
- **Equipments:**
  - Zanasi or Mertalli – Dosator (hollow tube).
  - Hoflinger-Karg – Tamping pins.

  Weight variation problem can be encountered with these two methods.

  Overly lubricated granules – delaying disintegration.

- Humidity affects moisture content of:
  - Granulation
  - On empty gelatine capsules.
- **At high humidity:** Capsule swells make separation of the capsule parts difficult to interfere with the transport of the capsule through the process.
- **At low humidity:** Capsule brittle increased static charge interferes with the encapsulation operation.

Examination of the formula to determine:

1. Ability to withstand batch-scale.
2. Process modification.
3. Compatibility of the equipment with the formulation.
4. Cost factor.
5. Physical space required.
6. Market requirement.
7. Layout of the related functions.
8. Availability of the raw materials meeting the specifications.

1.11 SCALE-UP LIQUID ORALS

1. The physical form of a drug product that is pourable displays Newtonian or pseudo plastic flow behaviour and conforms to its container at room temperature.
2. Liquid dosage forms may be dispersed systems or solutions.
3. In dispersed systems there are two or more phases, where one phase is distributed in another.
4. A solution refers two or more substances mixed homogeneously.

Steps in Liquid Manufacturing Process:

1. Planning of material requirements.
2. Liquid preparation.
3. Filling and packing.
4. Quality assurance.

Critical Aspects of Liquid Manufacturing:

1.11.1 Formulation Aspects of Suspensions

Sr. No.	Purpose	Agent
1.	Facilitating the connection between API and vehicle.	Wetting agents.
2.	Protecting the API.	Buffering-systems, polymers, antioxidants.
3.	Maintaining the suspension appearance.	Colourings, suspending agent, flocculating agent.
4.	Asking the unpleasant taste/smell.	Sweeteners, flavourings.

1.11.2 Formulation Aspects of Emulsions

Sr. No.	Purpose	Agent
1.	Particle size	Solid particles, droplet particles
2.	Protecting the API	Buffering-systems, antioxidants, polymers
3.	Maintaining the appearance	Colourings, emulsifying agents, penetration enhancers, gelling agents
4.	Taste/smell masking	Sweeteners, flavourings

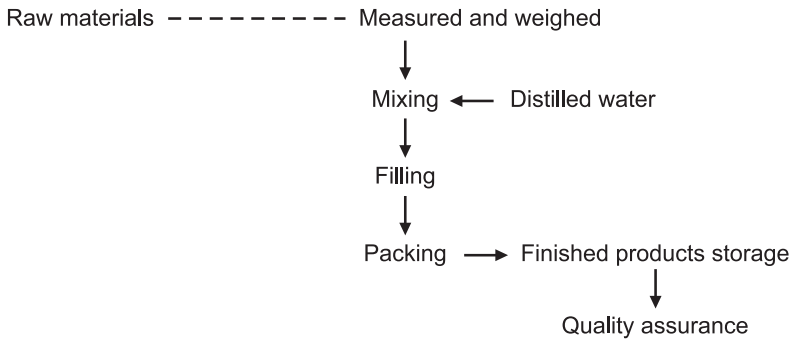
1.11.3 Formulation Aspects of Solutions

Sr. No.	Purpose	Agent
1.	Protecting the API.	Buffers, antioxidants, preservatives.
2.	Maintaining the appearance.	Colourings, stabilizers, co-solvents.
3.	Antimicrobial.	Preservatives.
4.	Taste/smell masking.	Sweeteners, flavourings.

Equipments Used:

1. Mixer
2. Homogenizer
3. Filtration assembly
4. Bottling assembly

General Flow Chart for Manufacturing Liquid Orals:



Quality Assurance:

- Dissolution of drugs in solution
- Potency of drugs in suspension
- Temperature uniformity in emulsions
- Microbiological control
- Product uniformity
- Final volume
- Stability

1.12 SEMI-SOLID DOSAGE FORMS

- In general, semisolid dosage forms are complex formulations having complex structural elements.
- Often, they are composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase.
- The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system.

Parameters:

1. For a true solution, the order in which solutes are added to the solvent is usually unimportant.
2. The same cannot be said for dispersed formulations, however, because dispersed matter can distribute differently depending on to which phase a particulate substance is added.
3. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added.
4. This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed.
5. Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product.
6. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (for example, homogenization).
7. Aging of the finished bulk formulation prior to packaging is critical and should be specifically addressed in process validation studies.

1.13 PILOT PLANT OPERATION

Validation:

1. Design specification.
2. Installation qualification.
3. Operational qualification.
4. Performance qualification.
5. Compliance with cGMP and FDA standards.

Training:

1. Technical skills and knowledge.
2. Safety and environment responsibility.
3. Compliance with GMP.
4. Compliance with SOPs.

Engineering Support:

1. Design of facility.
2. Co-ordination scheduling.
3. Direction of ongoing operations.
4. Validation of facility.
5. Construction of facility.

Maintenance and Calibration:

1. To ensure the integrity and equipment reliability and research.
2. To meet cGMP norms.

Computerized System:

1. Material control
2. Labelling (GMP-GLP)
3. Inventory
4. Orders (FIFO)

Process and Manufacturing Activities:

1. Formulation and process development studies.
2. Technology evaluation scale up and transfer.
3. Clinical supply and manufacture.

Quality Assurance:

1. Auditing pilot plant.
2. Auditing and approval of component supplies.
3. Reviewing approval and mainframe batch records for clinical supplies.
4. Sampling and release of raw material.
5. Release of clinical supplies.
6. Maintaining and distributing facility and operating procedure (SOPS).
7. Review and approval of validation.
8. Engineering documentation.

Quality Control:

1. Release testing of finished product.
2. Physical, chemical and microbiological testing of finished clinical products, components required for supplies.
3. Testing for validation and revalidation.
4. QC in process testing during development scale-up and technology transfer.

Plant: It is a place where the 5M'S like money; material men, method and machine are brought together for the manufacturing of the products.

1. Last 25-30-year pharmaceutical researches are going in an advanced manner.
2. Have witnessed amazing invention and innovation in pharmaceutical field.
3. NDA and ANDA are all time high.
4. Researchers are motivated to adopt new processes and technology.
5. Scale-up batches are essential for ensuring success in the clinical testing and bioequivalence study.
6. Pilot plant scale-up is one of the most important stages in the product development.

1.14 SCALE-UP and POST APPROVAL CHANGES (SUPAC)

FDA and American association of pharmaceuticals scientist (AAPS) provided the scientific foundation for the scale-up and post approval changes required for immediate release product called SUPAC.

It provides guidelines for post approval changes in the following:

- Components
- Compositions
- Site of manufacturing
- Process and equipment

Significance of Pilot Plant:

1. Examination of formulae.
2. Review of range of relevant processing equipments.
3. Production rate adjustment.
4. Idea about physical space required.
5. Appropriate records and reports to support GMP.
6. Identification of critical features to maintain quality.

Advantages:

1. Members of the production and quality control divisions can readily observe scale-up runs.
2. Supplies of excipients and drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division.
3. Access to engineering department personnel is provided for equipment installation, maintenance and repair.

Disadvantages:

1. The frequency of direct interaction of the formulator with the production personnel in the manufacturing area will be reduced.

2. Any problem in manufacturing will be directed towards its own pilot-plant personnels.

General Stability Consideration:

The effect that SUPAC changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.

For SUPAC submissions, the following points should also be considered:

1. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.
2. Where stability data show a trend towards more potency loss or degrading under accelerated conditions, it is recommended that historical accelerated stability data from a representative perchance batch be submitted for comparison.
3. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement.
4. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.

1.15 INTRODUCTION TO PLATFORM TECHNOLOGY

Platform technologies are considered a valuable tool to improve efficiency and quality in drug product development. The basic idea is that a platform, in combination with a risk-based approach, is the most systematic method to leverage prior knowledge for a given new molecule. Furthermore, such a platform enables a continuous improvement by adding data for every new molecule developed by this approach, increasing the robustness of the platform. The technology has distinct and differentiating competitive advantages. It can significantly improve the bioavailability of complex molecules due to its sub-micrometric size and adhesive systems for a higher time of contact to skin. It is also flexible, encapsulating a broad range of active principles and its systems can be adjusted to achieve desired properties.

In addition, the technology is robust and versatile, with key features such as:

- Chemical stability and solubility of the active molecule.
- High drug loadings can be achieved.
- High encapsulation efficiency.
- Developed industrial process and scalability.
- Stable, simple and solvent-free technologies.
- Reformulation of drugs near patent expiration.
- Development of drugs previously thought impossible.
- New administration routes for a variety of molecules.

QUESTIONS

Multiple Choice Questions:

1. Which of the following is not a scale-up process?
   (a) Laboratory to pilot-scale (b) Pilot-scale to industrial-scale
   (c) Industrial to pilot-scale (d) Laboratory to industrial-scale
2. Pilot plant can be used for ……
   (a) Evaluating results for laboratory studies
   (b) Product and process correction
   (c) Shelf life and stabilities studies
   (d) All of above
3. What does the expansion in CRO's reflect?
   (a) A pharma company's desire to balance control over drug development with fluctuations in workload.
   (b) The pharma company trying to reduce its fixed investment in development by buying CROs.
   (c) The desire to reduce competition with smaller biotech companies.
   (d) A desire for the pharma companies to build their in-house development capability.
4. Which of the following methods are generally used in liquid filling?
   (a) Gravimetric (b) Volumetric
   (c) Constant level method (d) All the above
5. The filling method of a pharmaceutical liquid depends on the following factors ……
   (a) Viscosity of the liquid
   (b) Surface tension of the liquid
   (c) Compatibility with the material used in the construction of the filling machine
   (d) All the above

ANSWERS

1. (c)	2. (d)	3. (a)	4. (d)	5. (d)

Long-Answer Questions:

1. What do you mean by pilot plant scale-up? Give examples.
2. What is the significance of pilot plant scale-up with routine production procedure?
3. Explain the procedure for pilot plant scale-up for liquid orals.
4. Explain the procedure for pilot plant scale-up for semisolid dosage form.
5. Explain the procedure for pilot plant scale-up for liquid dosage form.
6. What do you mean SUPAC?
7. Write a short note on pilot plant scale-up for solid dosage form.

***

Chapter ... 2

TECHNOLOGY DEVELOPMENT AND TRANSFER

♦ **LEARNING OBJECTIVES** ♦

After completing this chapter, students will be able to understand:

- Different terminologies of Technology Transfer (TT)
- Basic principles of TT
- TT protocols
- Information required for TT
- Agencies for Technology Transfer in India

2.1 WHO GUIDELINE FOR TECHNOLOGY TRANSFER (TT)

Technology transfer (TT) is a structural guideline which is intended for quality of the process, products, standardization and cost-effective productions.

This is a systematic process in which knowledge and experience are gathered and documented during life cycle of products originated from development, manufacturing, production and marketing or commercialization and are transferred to an authorized and accountable organization. TT is a fundamental part of discovery and development of newer pharmaceutical products and dosage forms.

As per World Health Organization, technology transfer is defined as, "A logical procedure that controls the transfer of any process together with its documentation and professional expertise between development and manufacture or between manufacture sites."

In Pharmaceutical industry, TT is involved in drug discovery, product development, clinical trials and full-scale commercialization.

2.2 DIFFERENT TERMINOLOGIES OF TECHNOLOGY TRANSFER (TT)

1. **Active Pharmaceutical Ingredients (API):** Any ingredients or substances which are used in the manufacturing of a pharmaceutical formulation and are considered as active ingredient of that dosage forms, are called as Active Pharmaceutical Ingredients (API).

2. **Change Control (CC):** Change control can be defined as, "A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipments or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state." (EU GMP Guidelines, Annexure 15).
3. **Control Strategy:** The proper sets of control obtained from product and process understanding to assure the process performance and product quality which include parameters of products, materials, drug substances, facilities, equipment availability, standardization process, in process control, quality of finished goods, etc.
4. **Critical Control Point (CCP):** Some controls are mandatory in the pharmaceutical industry to eliminate or to reduce the quality hazards. CCP is a step at which this control can be applied.
5. **Corrective Actions (CA):** Corrective actions are taken at CCP while controlling the quality hazards.
6. **Quality Assurance (QA):** According to WHO "Quality Assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.
7. **Quality Control (QC):** QC is that part of GMP concerned with sampling, specification, testing, documentation and release procedures which ensure that the necessary and relevant tests are performed, and the product is released for use only after ascertaining its quality.
8. **Design Qualification (DQ):** DQ is a documented verification of the proposed design of the facilities, systems and equipment that are suitable for the intended purpose.
9. **Installation Qualification (IQ):** IQ is an evidence of all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification.
10. **Operational Qualification (OQ):** OQ is established by objective evidence process for the control limits and action levels in product of all predetermined requirements.
11. **Performance Qualification (PQ):** PQ is established by verifying a process, under anticipated condition, consistently produces a product which meets all predetermined requirements.
12. **Drug Master File (DMF):** It is detailed information of a specific facility, process or product which has been submitted to Medicines Regulatory Authority (MRA) for the incorporation into the application for the marketing-authorization.

13. **Finished Pharmaceutical Product (FPP):** A finished pharmaceutical product will be considered as a product which contains one or more APIs and has undergone all steps of production, standardization, packaging, storing and labeling.
14. **Technology Transfer: Inter-Company Transfer:** The transfer of technology between sites of different companies is called as intercompany transfer.
15. **Technology Transfer: Intra-Company Transfer:** The transfer of technology between sites of same group of companies is called as intracompany transfer.
16. **Standard Operating Procedure (SOP):** It is an authorized written procedure with detailed instruction for the operation of equipment, maintenance of equipment, cleaning of equipment, validation of equipment, environmental control, sampling and analytical procedures.
17. **Technology Transfer Report (TTR):** A documented report of technology transfer consists of:
    - Procedures
    - Acceptance criteria
    - Obtained results
    - Conclusions
    - Deviations, if any
18. **Sending Unit (SU) and Receiving Unit (RU):** The discipline of any organization involved in transferring of designated process or method is called as sending unit (SU) and the organization involved in receiving the same is mentioned as receiving unit (RU).

2.3 GENERAL PRINCIPLES OF TECHNOLOGY TRANSFER (TT)

The basic requirements of TT are:

- Quality Risk Management (QRM)
- Documented approach
- Logical approach
- Skilled and trained staff
- Sending Unit (SU)
- Receiving Unit (RU)

The following general principles are to be followed for the successful TT:

- The project should attain the quality parameters based on QRM.
- The facilities and equipments available in SU and RU should be similar.
- The trained and skilled staffs should be available at RU.
- RU should reproduce the documented evidence of transferred product, process or manufacturing method against the predetermined specifications of SU.
- Reporting of out of specifications results and errors by the RU to SU.
- The clarity of transfer process should be maintained.
- The legal implications like royalties, intellectual property rights, conflict of interests should be conveyed prior and during the transfer.

2.4 TECHNOLOGY TRANSFER PROTOCOLS

The transfer process should be managed by SU, RU and if required, an additional agency in which proper directions and approvals are provided. There should be a proper management plan and formal agreements for the successful technology transfer.

The following steps should be followed as per the transfer protocol.

- Purpose and objective of the transfer.
- Scope of the transfer.
- Skilled personnel and their responsibilities.
- Comparison of materials, equipments and methods between SU and RU.
- Documented evidence of each stage of process control and critical stages.
- The transfer of documents should be achieved satisfactorily.
- Assessment of CCP (critical control points).
- Assessment of experimental process for manufacturing.
- Experimental process assessment for standardization and analysis.
- Information of different batches.
- Process validation.
- Assessment of out of specification or deviated results and change control.
- Analysis of finished products.
- Documented reports of analysis.
- Retention of reference materials, active ingredients, intermediate products and finished products.
- Approval of competent authorities or project manager.

2.5 QUALITY RISK MANAGEMENT (QRM)

2.5.1 Introduction

In the life-cycle of any pharmaceutical product the quality aspect is very important. The risk of quality variation in the pharmaceutical product can be assessed, controlled and communicated by a systematic process called QRM. It has been mentioned in ICH guideline Q9.

2.5.2 Principle

The basic principle of QRM is the assessment and evaluation of the associated risks based on scientific knowledge and evidence to maintain the quality of the product and customer satisfaction.

2.5.3 QRM Process

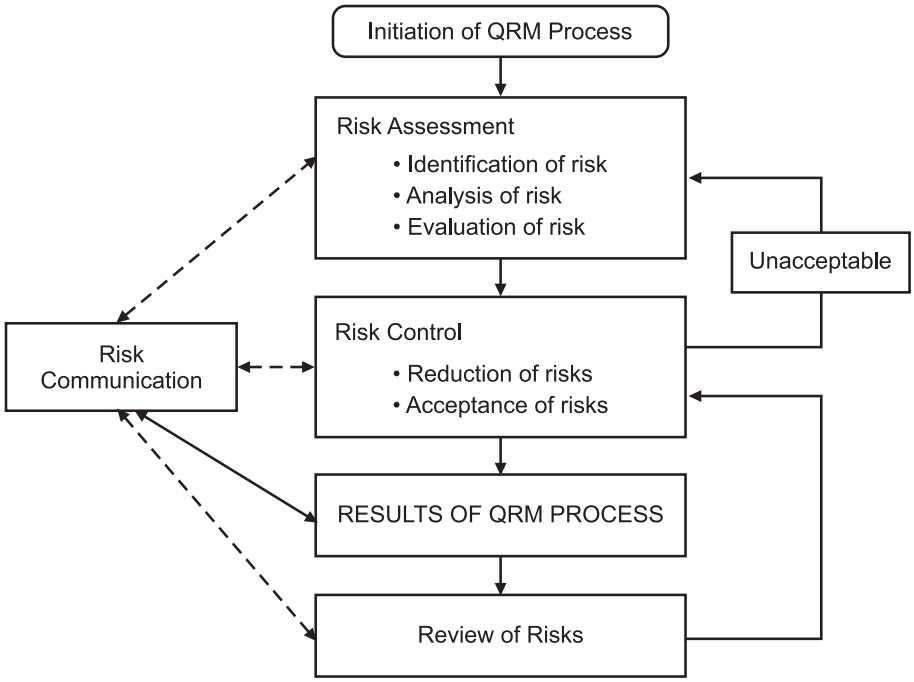


Fig 2.1: Process chart of QRM

The process of QRM can be summarized in following different steps (**Fig. 2.1**):

Step (1) QRM initiation:

To initiate the process of QRM the following plan can be followed:

- Types of risk and problem.
- Questions regarding risks.
- Information regarding quality and potential hazards.
- Information of background and raw data.
- Assessment of required resources.
- Specification of time limit.

Step (2) Risk Assessment:

This may include the following:

- **Identification of Hazards:** Systematic process to identify the risks and hazards.
- **Analysis of Risks:** Qualitative and quantitative estimations of hazards.
- **Evaluation of Risks:** Comparison of identified and analyzed hazards.

Step (3) Risk Control:

The basic purpose of risk control is to reduce or eliminate the risks. It should be based on the following points:

- The acceptance level of risks.
- Possible steps to reduce or eliminate the risks.
- Balance among benefits, risks and resources.

(a) Reduction of Risks: The level of risk when exceeds the acceptance criteria, the reduction of risks should be followed. Detection of risks, risks assessment and the process control can reduce the level of risks.

(b) Acceptance of Risks: It is the decision to accept the risk.

Step (4) Results of QRM and Risk Reviews:

The review of result obtained from the QRM process is a part of quality management system. Results of QRM process should be documented, reviewed, inspected, audited and possible change control is suggested. The unsatisfactory review process will suggest the failure of the investigation and the process can be started from risk assessment step.

Step (5) Risk Communication:

This is the communication process of the data of risk management system. The risk management system can be communicated at any step of risk management process (Risk assessment, control and review process, in Fig. 2.1 mentioned as dotted line). The well documented result of QRM process should be submitted and communicated (in Fig. 2.1 mentioned as solid line) to the parties.

This guideline is very important in pharmaceutical industry with respect to QRM. The process is applicable for the pharmaceutical product from manufacturing to inspection process.

2.6 INFORMATION REQUIRED FOR TECHNOLOGY TRANSFER

For the technology transfer from research and development section to production, the RU should be capable of performing and accommodating the production capacity. The detailed process development should be transferred. At RU, expert personnel and facility available at the site are the primary considerations. Development of protocol by SU and RU jointly for the technology transfer is necessary.

2.6.1 Starting Materials

For the process of successful technology transfer to the production, the specifications and characteristics of starting materials like API and excipients should be identical at both the place SU and RU.

2.6.1.1 Active Pharmaceutical Ingredients (API)

The complete API master file, Drug Master File (DMF) and relevant auxiliary information of API which are important for the manufacturing process should be provided by the SU to RU. Some important information is mentioned below:

- Details of API manufacturer and supplier.
- Detail scheme of synthesis, process outline, raw materials, process control.

- Details of intermediate products.
- Complete information of API for formulation process. It includes:
  - Physicochemical parameters like solubility, partition coefficient (method of determination).
  - Particle size distribution.
  - Bulk and tap density with detail method of evaluation.
  - Disintegration profile.
  - Nature of hygroscopicity.
  - Water content.
  - Loss on drying.
  - Limit of impurities.
- Microbiological factors.
- Environmental factors.
- Pharmacopoeial standards with method of determination.
- Stability studies.
- Storage and handling guidance mentioned in Pharmacopoeias.

2.6.1.2 Excipients

The excipients used in the process of manufacturing have an important role in quality of the finished product. The duty of SU is to provide detail information of excipients to RU. The following information is some of the examples of detail information:

- Details of manufacturer and supplier.
- Category of excipients.
- Dosage form available.
- Descriptions.
- Solubility.
- **For transdermal dosage form:**
  (a) Lipophilicity, Partition coefficient
  (b) Particle size and distribution
  (c) Specific gravity
  (d) Water content and loss of drying
  (e) Dissolution rate with detail process
- **For solid dosage form:**
  (a) Bulk and tap density profile with detail method of evaluation
  (b) Compaction properties
  (c) Particle size and distribution
  (d) Water content and loss of drying
  (e) Nature of hygroscopicity

- **For semi-solid dosage form:**
  (a) Melting point
  (b) Range of pH
  (c) Viscosity
  (d) Specific gravity
- **For liquid dosage form:**
  (a) Range of pH
  (b) Viscosity
  (c) Specific gravity
  (d) Water content
- **For parenteral formulation:**
  (a) Range of pH
  (b) Viscosity
  (c) Specific gravity
  (d) Water content
  (e) Osmotic pressure
  (f) Ionic strength
- **For aerosol/inhaled dosage form:**
  (a) Solubility
  (b) Bulk and tap density
  (c) Particle size and distribution
  (d) Surface area
  (e) Water content

2.6.2 Process Information

Regarding the information of process and testing the following information should be provided by the SU.

(a) Requirement of facility.
(b) Requirement of equipments.
(c) Requirement of skilled person.
(d) Detail information of raw materials.
(e) Storage guideline and handling of raw materials and finished goods.
(f) Availability of all SOPs.
(g) Manufacturing process.
  - Process flow charts
  - Process optimization
  - Detail master batch records
  - Method of addition of raw materials and excipients
  - Details of intermediate products
  - Reaction conditions
  - Environmental factors

(h) Analytical methods
- Standardization process
- Assay procedure
- Finished goods testing

(i) Validation protocols
- Process validation
- Equipment validation

(j) Annual audits and reviews

(k) Change control, critical control point and corrective actions

(l) Quality control and assurance

2.6.3 Finished Products

A finished pharmaceutical product is a final product that has completed all stages of production and manufacturing. The finished product should be stored in specific container and proper labeling is mandatory. All the associated information in well documented manner should be informed and transferred from SU to RU. The finished product storage and handling guidelines are to be informed to RU along with the detail specification and analytical test procedures. The predetermined specifications should be analyzed and the detail standardization process should be transferred.

2.6.4 Packaging

Information regarding packaging of finished product should be transferred to RU. Some of the important instructions are given below:

- Suitable container
- Proper closure system
- Packing material
- Process of packaging
- Design of packaging
- Proper labeling
- Relevant information mentioned in package and label

The information provided by SU should be analyzed at RU for packaging either the packaging is suitable, safe, protective and compatible to the finished product or not. Packaging should be suggested in such a manner that the final product should not decompose or affected by the environmental factors. The product should not be oxidized and should be protected from sunlight. The formation of undesired substance can make the product spurious and toxic. The container should not react with the product and the efficacy of the product should not be altered by any means after packaging.

2.6.5 Documentation

Some of the important documents required in technology transfer are:

- Technology transfer protocol, qualification protocol and report.
- Training protocols and report.
- Standard Operating Procedure (SOP).
- Technology transfer report.
- Analytical methods transfer protocol.

- Validation report (VR).
- Process validation report.
- Cleaning validation protocol and report.
- Validation Master Plan (VMP).
- Master batch record.

For a successful technology transfer, the documents related to facility available at RU, detail description of manufacturing process, sampling procedures, approved SOPs for all instruments and process, information of storage, packaging, cleaning, validations, stability information and regulatory requirements should be provided by SU to RU before starting the productions.

2.6.6 Premises

The SU should make available the information regarding the layout and construction of buildings and services. The air-conditioning system, ventilation, temperature, humidity and compressed air related information should be provided to RU before the production. RU should include the risk management, safety requirements, emergency protocols and waste management provisions in the list of information.

2.6.7 Equipments

The SU should provide the following to RU regarding equipments:

- List of equipments required.
- Specific model and makers of equipments.
- Manuals and SOPs.
- Set-up, maintenance, calibration and storage protocol.
- IQ, OQ and PQ status.

2.6.8 Qualification and Validation

The qualification and validation protocol should be decided on the basis of QRM and should be provided by SU to RU in well documented manner.

2.6.9 Analytical Method Transfer

Analytical methods are used to analyze raw materials, finished products, packaging materials and cleaning samples. Analytical method transfer should be performed by providing all the information regarding analytical testing.

The SU should provide the following information for analytical method transfer:

- The methods of analysis and testing of raw materials, finished products.
- Training for analyst and staff.
- Details of equipments used for the testing.
- Testing parameters.
- Experimental principle, design and methods.
- Quality control testing results.
- Validation reports.

After getting all information from the SU, the RU should have some responsibilities for the successful analytical transfer, some of them are:

- Agreement in acceptance criteria.
- Review of analytical methods.

- Trained and skilled staffs.
- Availability of necessary equipments.
- Documents for recording the analytical results.
- Execution of transfer protocol.
- Proper validation to implement the process.
- Availability of Pharmacopoeias.

WHO has clearly mentioned about the possible experimental designs for analytical testing. The tests are:

- Identification test.
- Content uniformity.
- Solubility.
- Assay or percentage purity of the components.
- Dissolution parameter.
- Qualitative and quantitative tests for microbiological assays.
- Limit test for impurities.
- Residues recovery.

The responsibilities from both SU and RU should be performed and should prepare the report jointly to execute the transfer protocol.

2.7 AGENCIES FOR TECHNOLOGY TRANSFER IN INDIA

For the successful TT in India several agencies are working. Some of them are discussed below.

2.7.1 Asian and Pacific Centre for Transfer of Technology (APCTT)

APCTT is a United Nations Regional Institution that is governed by a Governing Council consisting of a representative designated by the Government of India. The agency is under the Economic and Social Commission for Asia and the Pacific (ESCAP). APCTT was established in 1977 in Bangalore. The main centre was moved to New Delhi in 1993.

APCTT governs TT to and from small and medium-scale enterprises in Asia and the Pacific. It regulates the development projects which are funded internationally to provide more strength for TT in Asia and the Pacific.

Technology transfer related areas of APCTT are institution building, human resources development, studies, business partnership development.

2.7.2 National Research Development Corporation (NRDC)

NRDC was established in 1953 by Govt. of India with the aim of promotion, development and commercialization of TT from public sector to private sector. NRDC is involved in transfer of technologies, inventions, patents and processes from the national research and development institutions and universities that are under the administrative control of the Department of Scientific and Industrial Research and Ministry of Science and Technology.

2.7.3 Technology Information, Forecasting & Assessment Council (TIFAC)

TIFAC, an autonomous organization, was established in 1988 under DST (Department of Science & Technology, Govt. of India). TIFAC is aimed to promote and support the technology, innovations in selected areas of national importance. TIFAC concentrates on technology innovation and development through various sustained programs

between industry and academia. TIFAC released its Vision 2020 under the leadership of Dr. APJ Abdul Kalam, the former chairman of TIFAC in 16 technology areas and in 2016 Vision 2035 prepared by TIFAC has been inaugurated by Hon'ble Prime Minister of India Shri. Narendra Modi in 12 thematic areas of national priorities and importance in Mysuru, Karnataka. The 12 thematic areas are:

1. Education
2. Medical Science and Health Care
3. Food and Agriculture
4. Water
5. Energy
6. Environment
7. Habitat
8. Transportation
9. Infrastructure
10. Manufacturing
11. Materials
12. Information and Communication Technologies (ICT).

2.7.4 Biotech Consortium India Limited (BCIL)

BCIL, public limited company, was inaugurated in 1990 under the Indian Companies Act, 1956. BCIL is promoted by the Department of Biotechnology (DBT), Ministry of Science and Technology, Government of India and All India Financial Institutions. BCIL was aimed for providing the necessary linkages among stakeholders and business support to facilitate the acceleration of commercialization of biotechnology. BCIL assists scientists, technologies, research institutions, universities, first entrepreneurs, the corporate sector, national and international organizations, central government, various state governments, banks and financial institutions.

BCIL works in the following aspects:

- Technology transfer
- Project consultancy
- Fund syndication
- Information dissemination
- Manpower training and placement related to biotechnology

2.7.5 Technology Bureau for Small Enterprises (TBSE)

TBSE provides the opportunity to the small enterprises to at the global level for acquisition of technology or establish business collaboration. TBSE works under Development Commissioner, Ministry of Micro, Small and Medium Enterprises (MSME) and it is partially funded by office of Development Commissioner (DC), Small Scale Industries (SSI), and Government of India.

The important features of TBSE are:

1. TBSE offers a professionally managed system for technology and collaboration search.
2. TBSE builds up confidence between partners.
3. TBSE has proper mechanism for arranging technology and finance.
4. TBSE provides a gateway to global technology market through networking.
5. TBSE takes up project appraisal and preparation o business plan.

2.7.6 Small industrial Development Bank of India (SIDBI)

SIDBI was established on April 2, 1990, through an Act of Parliament, under the Department of Financial Services, Government of India. It is a development financial institution in India. The head quarter is situated at Lucknow, Uttar Pradesh. The purpose of SIBI is to provide refinance facilities and short term lending to industries, and serves as the principal financial institution in the Micro, Small and Medium Enterprises (MSME) sector.

2.8 TECHNOLOGY TRANSFER RELATED DOCUMENTS

2.8.1 Confidentiality Agreement

It is also called as non-disclosure agreement (NDA). It is used to protect the proprietary nature of the technology and retain the confidentiality of a technology or invention. The drafting of the appropriate clauses can be essential for the maintenance of the value of the technology. The need of this agreement is due to the increase in competition and the new technologies can be exploited. Thus it is necessary to obtain protection to the continuous innovation process through confidentiality agreements.

2.8.2 Licensing

The license agreement is generally referred to the licensing of intellectual property rights such as; patents, trademarks, copyrights, etc. This agreement has a role on maintaining the confidentiality and secrecy aspects of the contract.

2.8.3 MoUs

MoU stands for Memorandum of Understanding. It is a negotiated agreement and contract between the Government and the Management of the Central Public Sector Enterprise (CPSE). MoUs are used either when the parties do not imply a legal commitment or where the parties cannot create a legally enforceable agreement.

QUESTIONS

Multiple Choice Questions (MCQs):

1. MoU stands for …….
   (a) Memorandum of Ubiquitous (b) Memorandum of Understanding
   (c) Memorandum of Unpredictable (d) Memorandum of Unprofitable
2. The transfer of technology between sites of different companies is called as …….
   (a) Inter-company transfer (b) Intra-company transfer
   (c) Technology transfer (d) Technology transfer protocol
3. The basic requirement of Technology Transfer is …….
   (a) Sending Unit (SU) (b) Receiving Unit (RU)
   (c) Both (a) and (b) (d) None of these
4. The definition of Quality Risk Management (QRM) has been mentioned in ICH guideline …….
   (a) Q7 (b) Q8
   (c) Q9 (d) Q10

5. For liquid dosage form, which information is provided by SU to RU?
   (a) Range of pH and viscosity (b) Specific gravity
   (c) H_2O content (d) All of these
6. Small industrial Development Bank of India (SIDBI) was established on …….
   (a) April 2, 1990 (b) April 2, 1991
   (c) April 2, 1992 (d) April 2, 1993
7. Installation Qualification (IQ) is …….
   (a) A documented verification of the proposed design of the facilities, systems and equipments.
   (b) An evidence of all key aspects of the process equipment and ancillary system installation.
   (c) Objective evidence process for the control limits and action levels in product of all predetermined requirements.
   (d) Verifying a process, under anticipated condition, consistently produces a product which meets all predetermined requirements.
8. The discipline of any organization involved in transferring of designated process or method is called as …….
   (a) SU (b) RU
   (c) QRM (d) None

ANSWERS

1. (b)	2. (a)	3. (c)	4. (c)	5. (d)	6. (a)	7. (b)	8. (a)

Long-Answer Questions:

1. Define technology transfer. What is sending unit and receiving Unit? Write the principles of technology transfer.
2. Define the following terms:
   (a) API
   (b) Excipients
   (c) DQ, IQ, OQ and PQ
3. What is the information required for technology transfer of starting materials from SU to RU?
4. Write briefly on the information required for process and finished product.
5. Write a note on analytical method transfer and basic responsibilities of SU and RU.
6. Which agencies are working for Technology Transfer in India? Write about any two agencies.
7. What is QRM? Describe the principle and process of QRM.

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Chapter ... 3

REGULATORY AFFAIRS & REGULATORY REQUIREMENTS FOR DRUG APPROVAL

♦ LEARNING OBJECTIVES ♦

After completing this chapter, students will be able to understand:

- Introduction to regulatory affairs which include historical overview and current scenario.
- Regulatory authorities and their role and responsibilities in the RA department.
- Various regulatory requirements for drug approval which include Investigational New Drug (IND) Application and New Drug Application (NDA).
- Data Presentation for FDA Submissions, Management of Clinical Studies.

3.1 INTRODUCTION

The present scenario of the pharmaceutical industry is very well co-ordinated, efficient and docile as per international standards for the manufacturing of various types of Biological and Chemical drugs (which also include medical devices, traditional herbal products and cosmetics) used for the human consumption and veterinary purpose. Various challenges faced by the regulatory system result into current well-defined controlled regulatory framework. The impact of this framework consequences into systematic manufacturing and marketing of safe, effective and qualitative drugs. With the vast growth of pharmaceutical industry, the legislations from each region have become more and more complicated and created an urgent need for regulatory professionals.

Regulatory affairs is a dynamic and challenging profession which is developed from the desire of governments and act as an interface between the pharmaceutical company and the regulatory agencies in order to ensure public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

3.2 HISTORICAL ASPECT

During 1950s, multiple tragedies i.e. sulfanilamide elixir, vaccine tragedy and thalidomide tragedy have resulted in substantial increase of legislations for drug products quality, safety

and efficacy. This leads to tightening of norms for Marketing Authorization (MA) and Good Manufacturing Practices (GMPs).

The drug industry in India was at very primitive stage till 20th century. Most of the drugs were imported from foreign countries.

(a) 1900-1960:

Government passed the Poisons Act, 1919 to check and hold the control on cheap drugs available in market. This Act helps in the administered possession of substance or sale of substances as specified as poison. It also stated the safe and protected custody of the poisons, packaging and labeling of poisons, maximum quantity to be sold and inspection as well as examination of the poison sold by vendor during the year.

The Poisons Act was followed by The Dangerous Drugs Act, 1930 which includes the regulation of cultivation, manufacturing, possession and trade of opium.

In 1985, Dangerous Drugs Act, 1930 and Opium Act, 1878 was revoked by passing of the Narcotics and Psychotropic Substances Act.

Following acts and rules were passed during this era:

- **Drugs and Cosmetics Act, 1940:** This act regulates the manufacturing, distribution, import and sale of allopathic, homeopathic, unani and siddha drugs.
- **Drugs and Cosmetics Rules, 1945:** This act regulates manufacture of Ayurvedic drugs for sale only, and not for consumption and use or possession.
- **Pharmacy Act, 1948:** This law was amended in 1986 and it generally controls and regulates the profession of pharmacy in India.
- **Drugs and Magic Remedies (Objectionable Advertisements) Rule, 1955:** This rule regulates the advertisement of drugs in India.
- **Drugs Prices Control Order, 1955 (DPCO) (under the essential commodities Act):** DPCO was further amended in 1995. As per this rule, government has a jurisdiction to review and fix maximum sale price for bulk drugs as well as formulation.

(b) 1960-1970:

The Indian Pharmaceutical industry was not mature enough and major market share was dominated by MNC and very few Indian manufacturers were in competition. Focus on pure research and development was very little because of deficiency of patent protection. The low availability and high drug price is because majority shares depend upon the high drug import.

(c) 1970-1980:

Government took control for the medicines regulation and issued few acts and rules.

- **Indian Patent Act 1970** (which came in force on 20 April 1972 and replaced Indian Patents and Designs Act of 1911): It serves as the basis for patent protection in India.

Under this Act, product patent was not allowed but the process and method of manufacturing of Drug substance was allowed to get the patent.

- **Drug prices capped:** Drug Prices Control Order (DPCO) was introduced to control the high price against consumers.

(d) 1980-1990:

The Indian industry has started investing in process development of API and created production infrastructure for the same.

(e) 1990-2000:

A rapid expansion in domestic market has observed in pharmaceutical industry. The companies have started entering into Research and Development.

(f) 2000-2010:

This period is considered to be the Innovation and Research era. During these years, innovative research activity, patenting of the drugs formula, process, indication as well as merger of companies was started.

Patent Amendment Act 2005: Indian Government brought out the Patents (Amendment) Ordinance, 2004 to address the issues relating to the patent in the country which was later replaced by the Indian Patent (Amendment) Act, 2005. The new Act brought some crucial changes on the legal regime of patent protection so as to address patent issues in technology, chemicals and pharmaceuticals sectors.

Compulsory Licenses: Such licenses can be granted for manufacture and export of the drug products "to any country having insufficient or no manufacturing capacity, for the said product, to address public health problems".

Few names are given below:

- **Drugs and Cosmetics (First Amendment) Rules, 2011:** It mandates registration of Clinical Research Organization (CRO) for conducting Clinical Trials (CT).
- **Clinical Trial Registry-India (CTRI):** It has been set up by the ICMR's (Indian Council of Medical Research) National Institute of Medical Statistics (NIMS).
- **Pharmacovigilance Program of India (PvPI):** The Central Drugs Standard Control Organization (CDSCO) has launched Pharmacovigilance programme to assure drugs safety to Indian patients.

3.3 REGULATORY AUTHORITIES

The rules and regulations are being framed considering Global, Regional and National pharmaceutical trade as well as necessity of the drugs based on population of patient. Most of the national guidelines regarding the development and market authorization application of drug are based on Global and Regional Harmonized guidelines. Global Network regulatory is composed of the representatives of each country in the world. International Council for Harmonization (ICH) in collaboration with USA, EU and Japan issues Harmonized technical requirements for manufacturers to follow for Market Authorization Application (MAA).

Fig. 3.1: National Regulatory Authority

(a) Health Authority (HA): The Health Authority to prepare drug regulatory guidelines and guidance documents which are compliant and conformity to existing laws and regulations and also coordinate with Global and/or regional regulatory body and in consultation with Pharmaceutical Manufacturer's Association issues technical requirements and process for Marketing Authorization Approval.

(b) Pharmaceutical Industry: Manufacturer develops drugs according to regulatory necessity of quality, safety and efficacy and applies for Marketing Authorization

3.4 ROLE OF REGULATORY AFFAIRS DEPARTMENT

RA acts as the interface between the pharmaceutical industry and Drug Regulatory authorities across the world. This department mainly involved in the registration of the drug products in respective countries prior to their marketing.

- The Regulatory Affairs department is the first point of contact between the Ministry of Health/Government departments and the company.
- The pharmaceutical business is being regulated by Drug Regulatory Affairs through designing appropriate laws (rules) and enforcing the same to attain and brought up highest standard of quality into the Global Trade.
- To bring a new drug into the market, it takes many years and therefore it is very crucial that the process should be managed effectively from the starting of the process to the end, so that drugs can meet the regulatory requirements and allow a

favourable evaluation of quality, efficacy and safety to meet the shortest possible timeline.

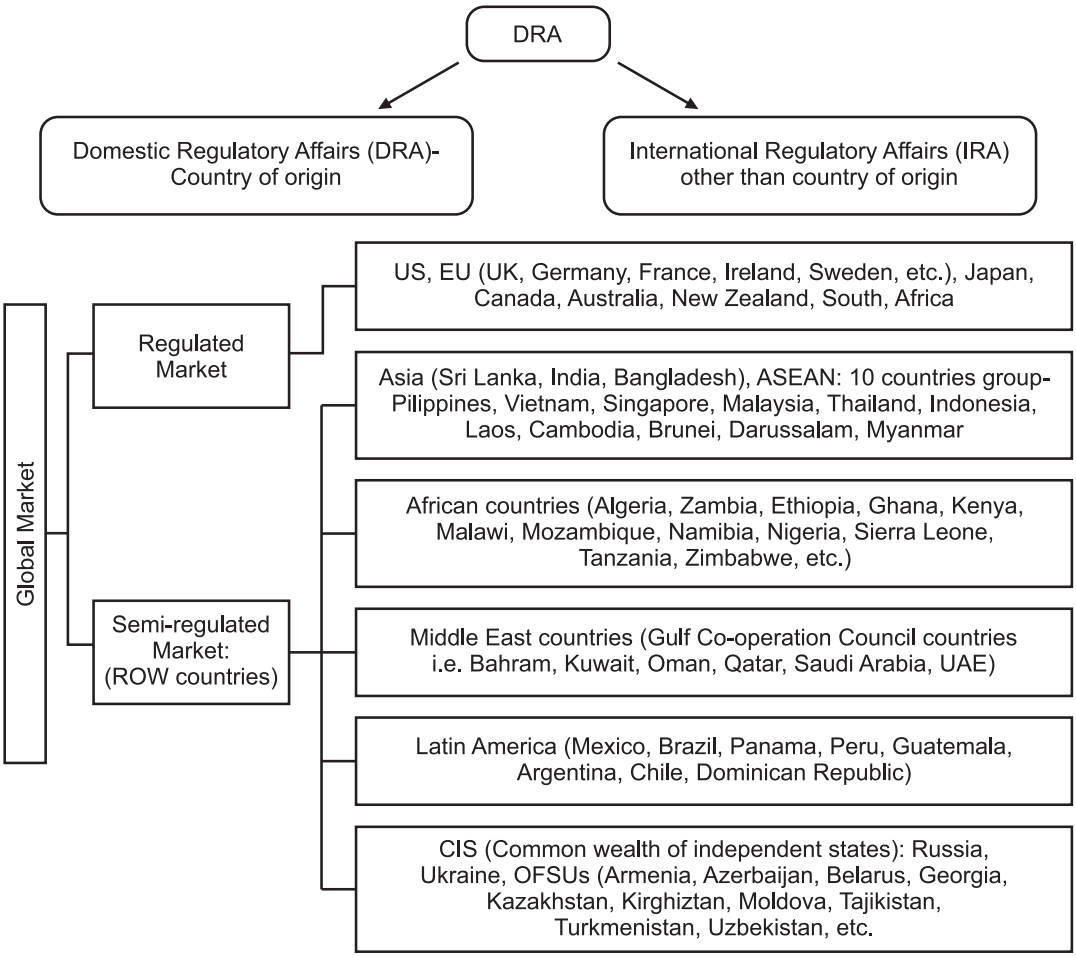

Fig. 3.2

- DRA professional plays the crucial role in each phase of drug development and post marketing activities.
- The pharmaceutical companies (DRA professionals of the company) accumulate all the date pertains to drug discovery and development stages and uses the same for the purpose of registration and marketing of drug.
- RA professionals of the company have to abide the array of strict and guidelines throughout the drug development process, to ensure the drug and efficacy of drugs in the humans.
- The Regulatory Affairs department also takes part in the drug development, marketing concepts and is a crucial requirement to approve the packaging and advertising of drug/product before it is used commercially.

3.5 RESPONSIBILITY OF REGULATORY AFFAIRS PROFESSIONALS

- The responsibility of RA is to ensure that their companies are complying with all of the system policy and laws pertaining to their business.
- Working with federal, state, and local regulatory agencies and staff on specific issues distressing their commerce i.e. working with Government agencies.
- RA advice their companies on the various aspects of regulatory affairs and particularly the climate that would affect proposed actions. (i.e. describing the "regulatory climate" in the region of issues such as the endorsement of prescription drugs).
- The Regulatory Affairs professional's job is to keep an eye on the ever-changing legislation in all the countries, particularly, where company have an interest to register their products.
- The RA professionals advice legally and technically at all stage both and help companies to save a lot of resources, time and money in drug development and its marketing.
- In any organization, the main responsibilities of the RA involve the preparation and presentation of registration documents to regulatory agencies and follow up all the process and discussion to obtain and maintain marketing authorization (MA) for the concerned products.

3.6 REGULATORY REQUIREMENTS FOR DRUG APPROVAL

Currently different nations have to follow different requirements for the regulatory approval of novice drug. It is almost difficult for every country to have the same regulatory approach for the Marketing Authorization Application (MAA), Therefore it is necessary to have knowledge about regulatory requirements for MAA of each country.

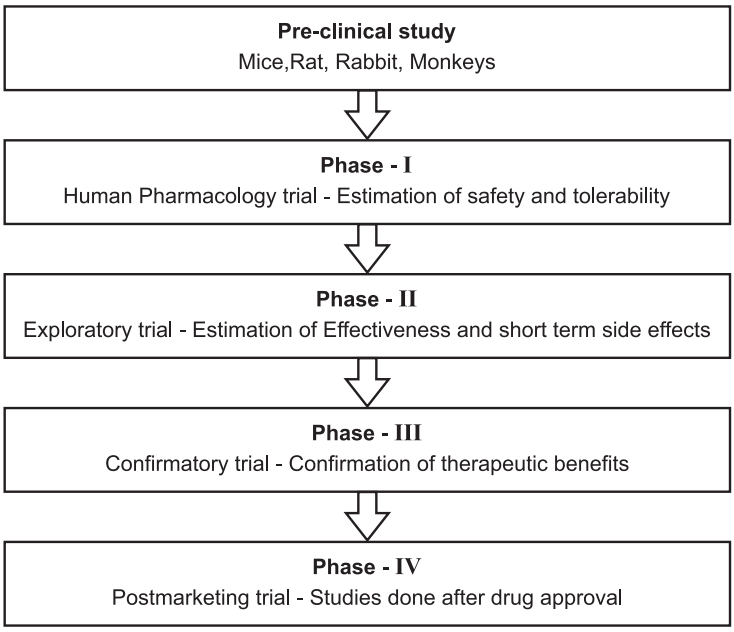

Fig. 3.3: Different phases of clinical trials

New Drug Application (NDA) is an application submitted to the respective regulatory authority for permission to market a new drug. To obtain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information and description of manufacturing procedures.

After agency received the NDA, it undergoes a technical screening. This process of evaluation is made to ensure that the sufficient date and the required information have been submitted in each area justifying the "filling" application form.

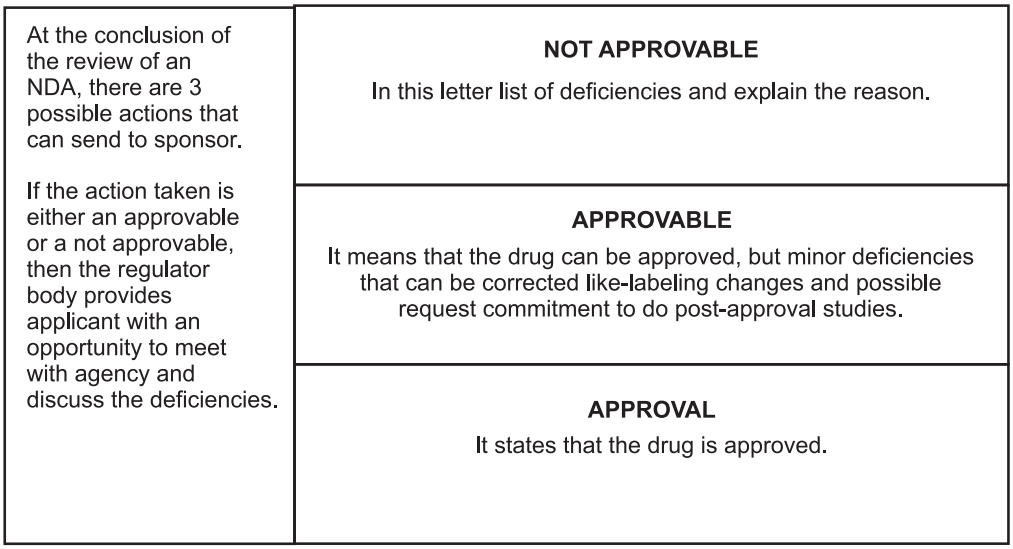

Fig. 3.4: Possible action after the review of NDA

3.7 DRUG DEVELOPMENT TEAMS

Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research on microorganisms and animals, filing for regulatory status, for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug.

The process of drug discovery and development is very long and needs 10-12 years which includes the close interaction of large number of scientific disciplines. Most biotechnology and pharmaceutical companies employ teams to mentor the process of various stages of drug development and making the drug candidate into therapeutic products.

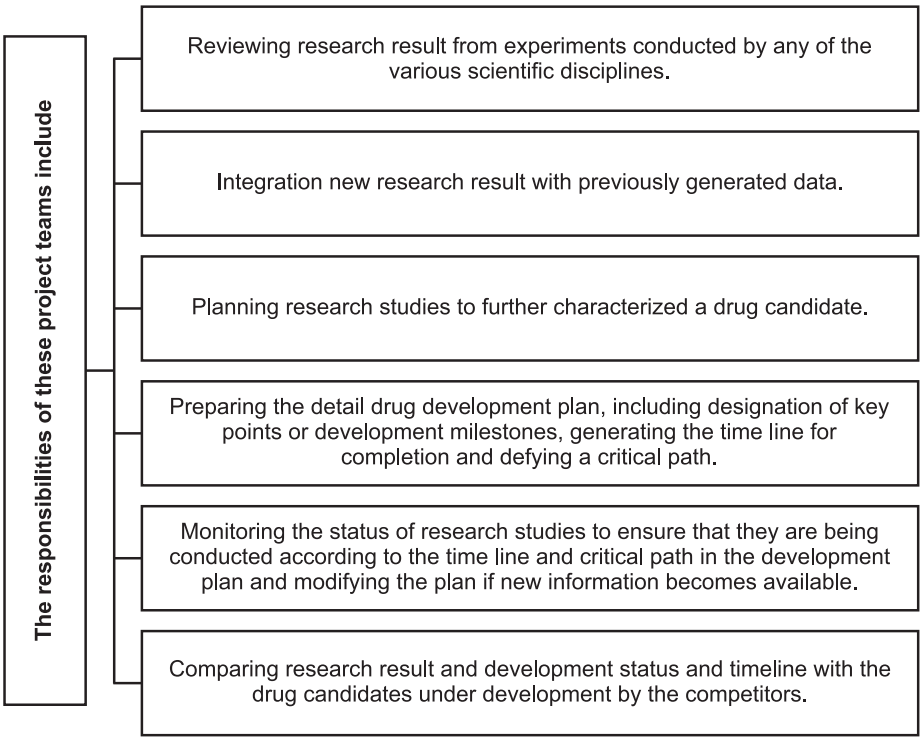

Fig. 3.5: The Responsibilities of these Project Teams

3.8 NON-CLINICAL DRUG DEVELOPMENT

Pre-clinical trial: A laboratory test for a novel drug or a new medical device is usually done on animal subjects, to see if the hoped-for treatment really works and if it is safe to test on humans.

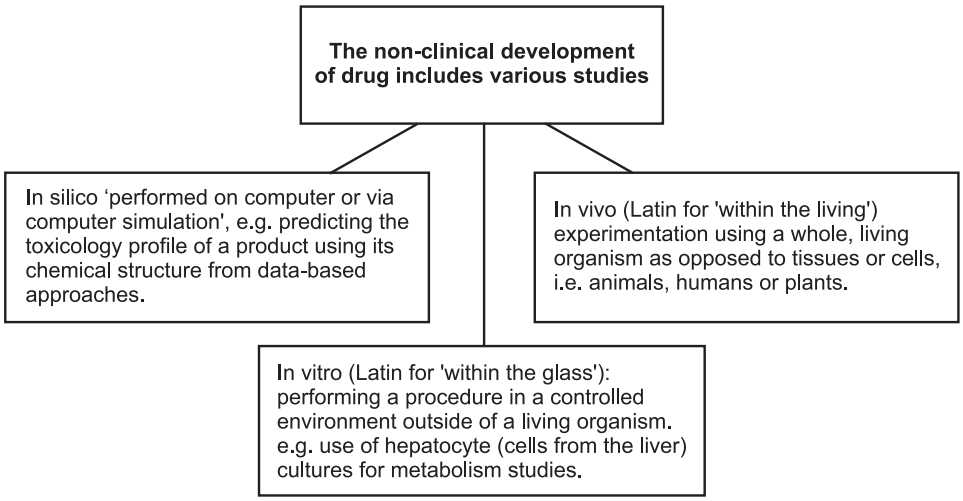

Fig. 3.6

The primary aims of the non-clinical (or pre-clinical) development phase is to analyze and determine which candidate has the greatest probability of success, assess its safety, and raise firm scientific foundations before transition to the clinical development phase. This process of non-clinical development of medicine is very complex, time consuming and regulatory driven. The selected candidate compound should also meet non-medical objectives, which also include defining the IPR and making enough medicinal products available for clinical trials.

Once identification of candidate compound is completed, the non-clinical development should start answering the following questions, and answers will come from specific assessments/studies:

- Does it work? → Assessment of Efficacy
- How will it be delivered and how will the body react? → Profiling
- Is it safe? → Toxicology/safety
- Is the manufacture viable and controllable?

Non-clinical development activities can continue throughout the life-cycle of the product.

3.9 VARIOUS PHARMACOLOGICAL APPPROACHES TO DRUG DISCOVERY

As an academic principle Pharmacology can be loosely defined as the study of effects of chemical substances on living systems.

This definition is so broad that it holds all the aspects of drug discovery, ranging from details of interaction between drug molecule and its target to consequences of placing the drug in the market.

Selectivity Testing: It consists of two main stages i.e. screening for selectivity and Binding assay. To determine the potency of drug, the selectivity of a compound for a chosen molecular target needs to be assessed.

Pharmacological Profiling: This includes the determination of pharmacodynamics effect of new compound, either on *in-vitro* models (which include cell lines or isolated tissues) or *in-vivo* models (which include normal animals, animal models of disease).

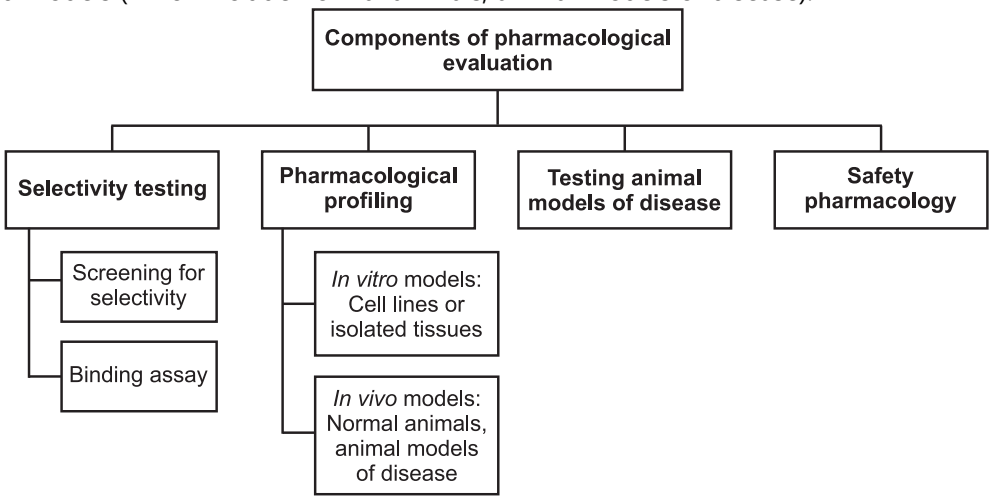

Fig. 3.7: Component of pharmacological evaluation

The aim of pharmacological profiling is to answer the following questions:

- Do the molecular and cellular effects measured in screening assays actually give rise to the predicted pharmacological effects in intact tissues and whole animals?
- Does the compound produce effects in intact tissues or whole animals not associated with actions on its principle molecular target?
- Is there a correspondence between potency of the drug at molecular level, tissue level and the whole animal level?
- Does *in-vivo* duration of action match up with the pharmacokinetic properties of the drug?
- What happens if the drug is continuously or repeatedly given to an animal over a course of days or weeks?
- Does it loose its effectiveness or reveal effects not seen on acute administration and whether there is any rebound after effect when it is stopped.

3.10 SAFETY PHARMACOLOGY

- This includes the scientific evaluation and study of potentially life threatening pharmacological effects of a potential drug which is unrelated to the desired therapeutic effect and therefore may present a hazard.
- These tests are conducted at doses not too much in excess of the intended clinical dose.
- Safety pharmacology seeks to identify unanticipated effects of new drugs on major organ function (i.e. secondary pharmacological effects).
- It is aimed at detecting possible undesirable or dangerous effects of exposure of the drug in therapeutic doses.
- The emphasis is on acute effects produced by single-dose administration rather than effects on chronic exposure as in toxicological studies.

3.11 TOXICOLOGICAL APPROACHES TO DRUG DISCOVERY

Acute Toxicity:

- Acute toxicity studies should be carried out in at least two species, usually mice and rats using the same route as intended for humans.
- In addition, at least two more routes should be used to ensure systemic absorption of the drug; this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration.
- The symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary.

Long-Term Toxicity:

- These studies should be carried out in at least two mammalian species and out of these two mammalian species one should be a non-rodent.
- The duration of study will depend on the factor that whether the application is for marketing permission or for clinical trial, and in the later case, on the phases of trials.
- If a species is known to metabolize the drug in the same way as humans, it should be preferred in long-term toxicity studies. The drug should be administered 7 days a week by the route intended for clinical use in humans.
- A control group of animals, given the vehicle alone, should always be included, and three other groups should be given graded doses of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it.

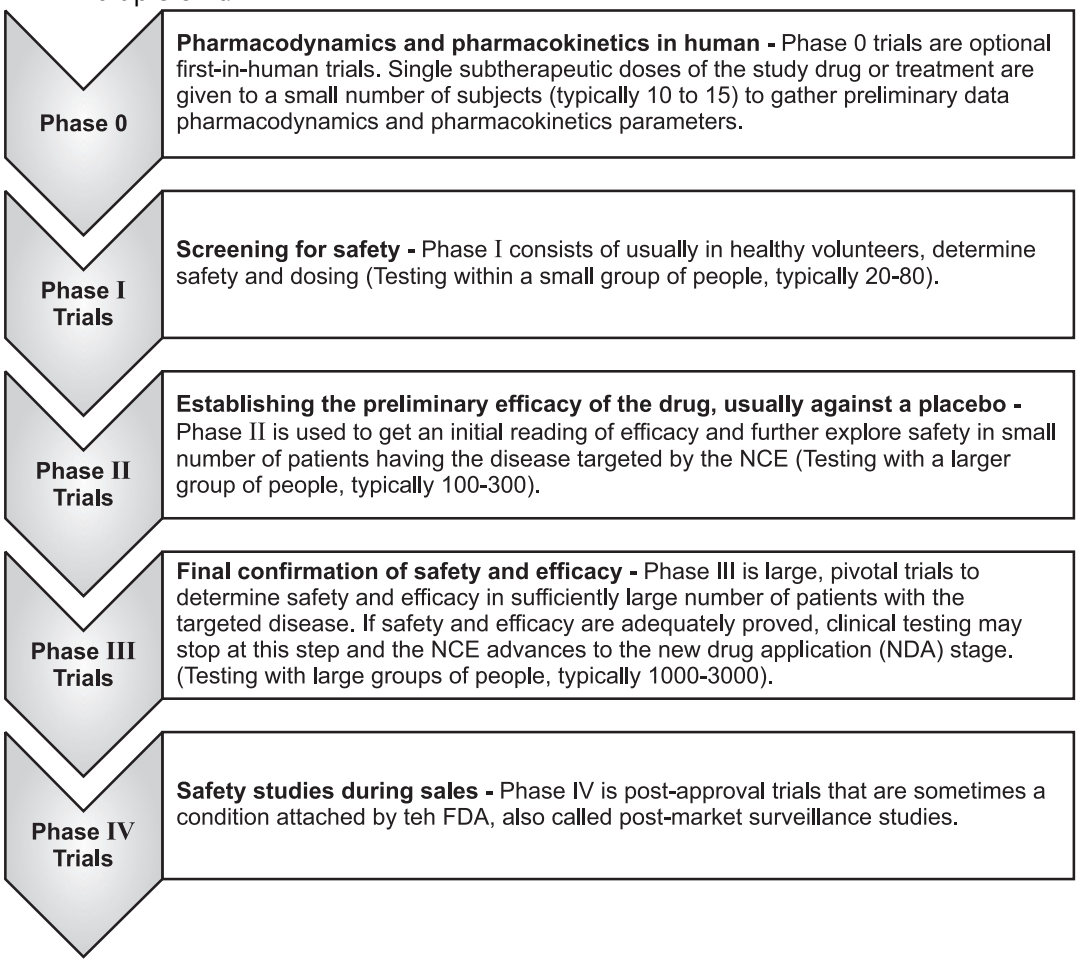

Fig. 3.8: Clinical Phases in New Drug Development

3.12 INVESTIGATIONAL NEW DRUG (IND) APPLICATION

Investigational New Drug (IND) is a program by which any pharmaceutical company can approach to obtain permission for the initiation of human clinical trials and to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved.

An investigational new drug (IND) application is to provide the data showing that it is reasonable to begin tests of a new drug on humans.

The IND application is also the vehicle through which a sponsor advances to the next stage of drug development known as clinical trials.

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines (Clinical Investigators).

Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement.

The IND application is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development.

When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans.

At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

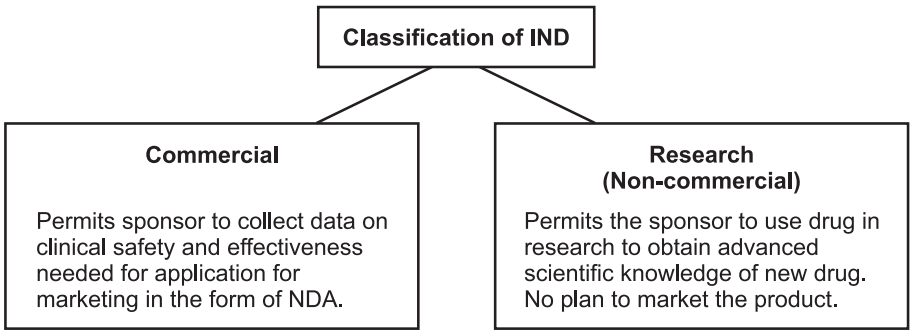

Fig. 3.9: IND Classification

3.13 TYPES OF IND APPLICATIONS

- Investigator IND application
- Emergency Use IND application
- Treatment IND application
- Screening IND application

1. Investigator IND Application:

In this an application is submitted by a physician, who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND application to propose studying of:

- An unapproved drug,
- An approved product for a new indication or
- An approved product in a new patient population.

2. Emergency Use IND Application:

This application allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND application, in accordance with 21CFR, Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist. In such a case, FDA may authorize shipment of the drug for a specified use in advance of submission of an IND application.

3. Treatment IND Application:

- This application is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.
- A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available.
- In the case of a serious disease, a drug ordinarily may be made available for treatment use during phase III investigations or after all clinical trials have been completed.
- In the case of an immediately life-threatening disease, a drug may be made available for treatment use earlier than phase III, but ordinarily not earlier than phase II.

4. Screening IND Application:

It is filed for multiple, closely related compounds in order to screen for the preferred compounds or formulations. The preferred compound can be developed under a separate IND. It can also be used for screening different salts, esters and other drug derivatives that are chemically different, but pharmacodynamically similar.

IND Review and Report: During this time, FDA has an opportunity to review the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. The report evaluates on the various factors like Medical Review, Chemistry Review, Pharmacology/Toxicology review, Statistical analysis and Safety review.

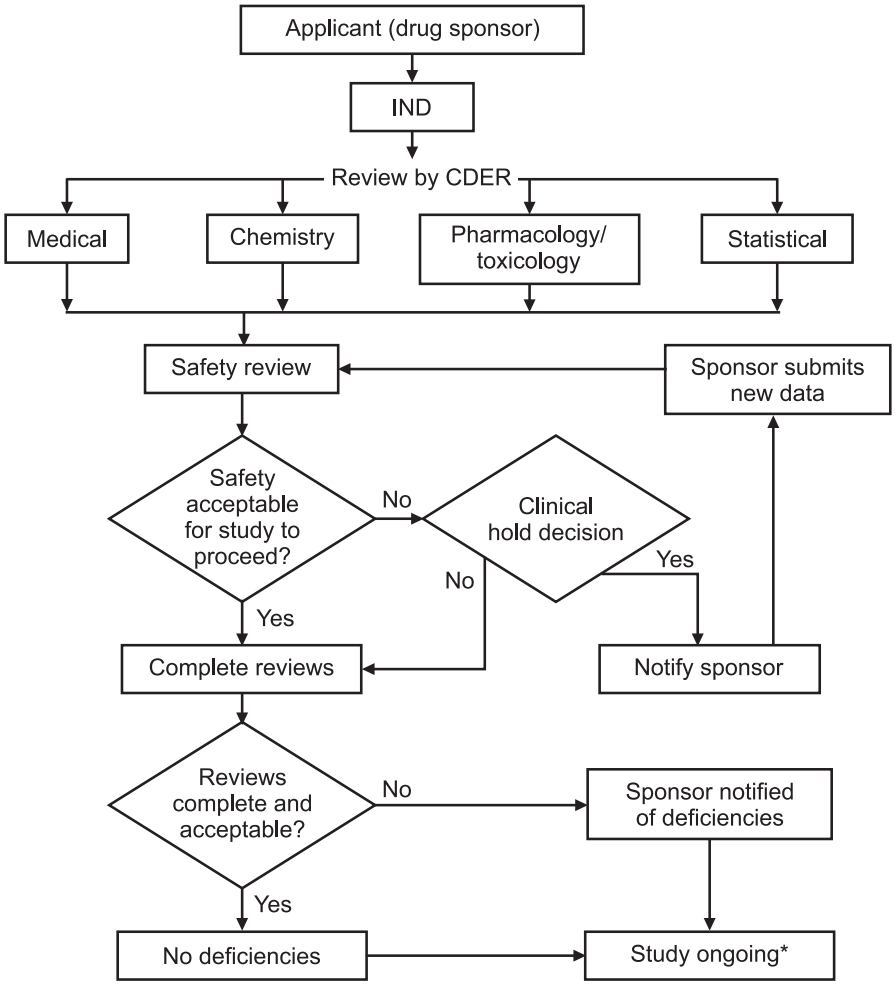

Fig. 3.10: Layout chart for IND Application

3.14 INVESTIGATOR'S BROCHURE (IB)

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subject.

3.14.1 Purpose of Investigator's Brochure (IB)

- Its purpose is to provide information to the investigators and others involved in the trial such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

- The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise and simple manner.
- IB enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk- benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB.

3.14.2 Contents of Investigator's Brochure

1. Table of contents.
2. **Summary** not exceeding 2 pages, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available of IP.
3. **Introduction:** Chemical name, active ingredients, pharmacological class, anticipated – therapeutic/diagnostic indication(s). General approach to be followed in evaluating the IP.
4. **Description of I.P.:** Physical, chemical and pharmaceutical properties of I.P. Storage and handling of I.P. Any structural similarity with the other known compound given.
5. **Non-clinical studies:** The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. The information provided may include: Species tested, Number of sex in each group, Unit dose (e.g., milligram/kilogram (mg/kg), Dose interval, Route of administration and Duration of dosing.
   - **5.1 Non-clinical Pharmacology:** A summary of the pharmacological aspects of the investigational product studied in animals should be included.
   - **5.2 Pharmacokinetics and Product Metabolism in Animals:** A summary of the pharmacokinetics (ADME) and biological transformation and disposition (getting a drug into its appropriate position in the body and in an appropriate concentration) of the investigational product in all species studied should be given.
   - **5.3 Toxicology:** (The study of the adverse effects of chemicals on animals): A summary of the toxicological effects found in relevant studies conducted in different animal species. (Single dose, Repeated dose, Carcinogenicity, Special studies (irritancy, sensitization), Reproductive toxicity).
6. **Effects in Humans:** A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, Pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. (a) Pharmacokinetics and Product Metabolism in Humans.

7. **Summary of Data and Guidance for the Investigator:** This section should contain non-clinical and clinical data of IP. IB provides the investigator a clear understanding of the possible risks, adverse reactions, observations and precautions needed for the clinical trial.

3.15 NEW DRUG APPLICATION (NDA)

The vehicle through which drug sponsors formally propose that the regulatory body approves a new pharmaceutical for sale and marketing, and the data gathered during the animal studies and human clinical trials of an investigational new product becomes a part of the NDA.

3.15.1 Aim of NDA

The aims of NDA include providing adequate information to permit FDA reviewers to establish the following:

- Safety and effectiveness of drug,
- Benefits overweigh risks,
- Is the drug's proposed labeling (package insert) appropriate, and what should it contain?
- Are the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug's quality adequate to preserve the drug's identity, strength, quality, and purity? Risk Benefit.

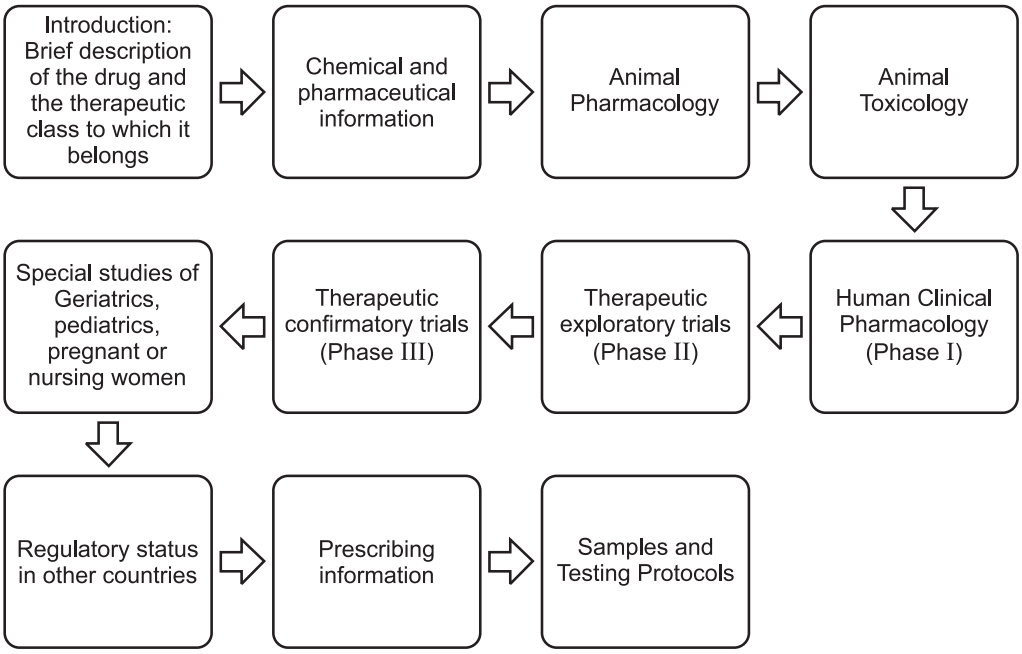

Fig. 3.11: NDA Contents

3.15.2 NDA Review Process

Once the application is submitted, the FDA has 60 days to conduct a preliminary review which will assess whether the NDA is "sufficiently complete to permit a substantive review".

If everything is found to be acceptable, the FDA will decide if the NDA will get a standard or accelerated review and communicate the acceptance of the application and their review choice in another communication known as the 74-day letter.

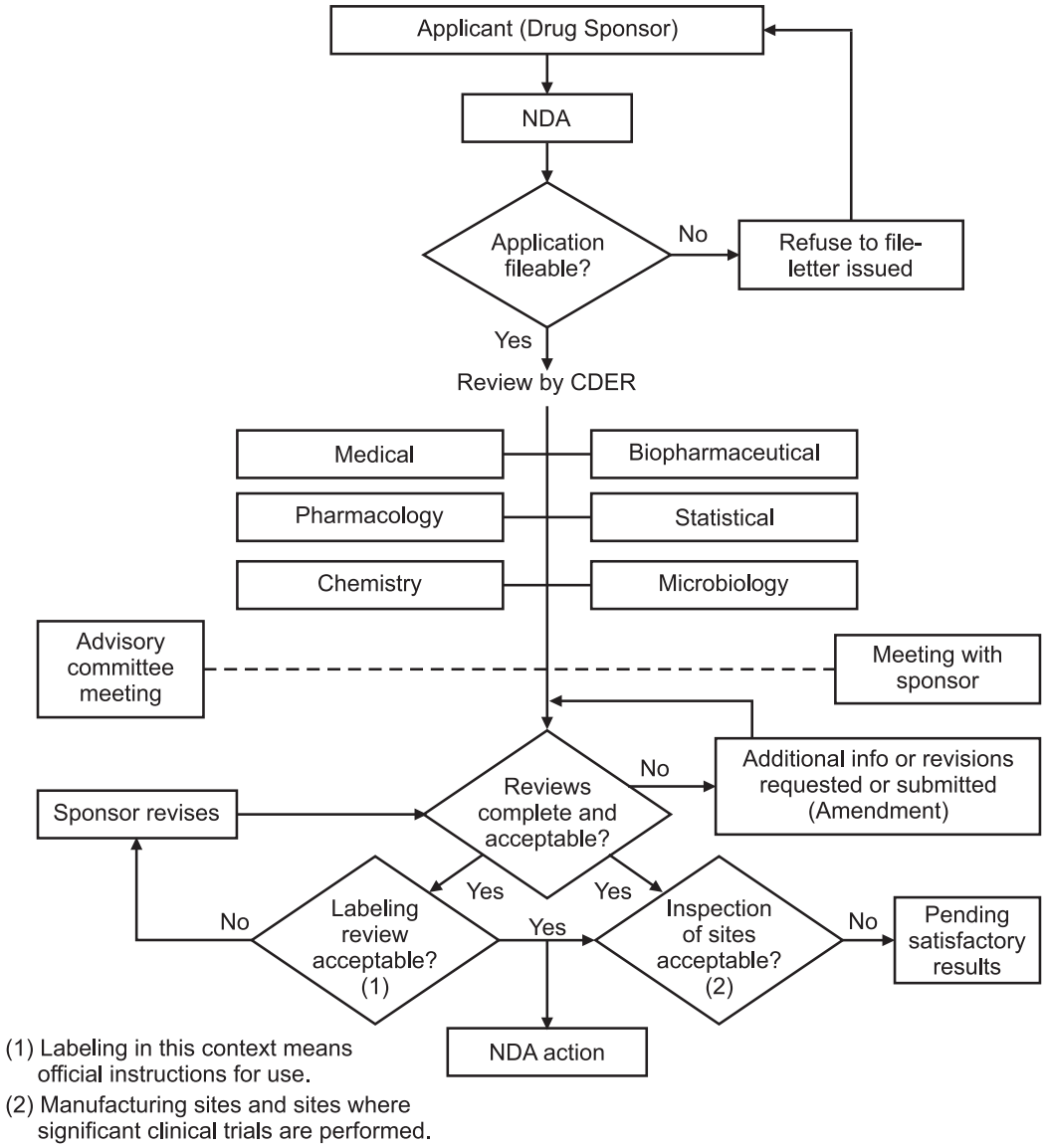

Fig. 3.12: NDA Review Process

3.16 BIO EQUIVALENCE STUDIES

BE studies are very essential to ensure uniformity in standards of quality, efficacy and safety of pharmaceutical products so that reasonable assurance can be provide for the various products containing same active ingredient, marketed by different licensees are clinically equivalent and interchangeable. Both Bioavailability and Bioequivalence focus on release of drug substance from its dosage form and subsequent absorption in circulation. Similar approaches to measure bioavailability should be followed in demonstrating bioequivalence.

Bioavailability: Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Equivalence: It is a relative term that compares drug products with respect to a specific characteristic or function or to a defined set of standards.

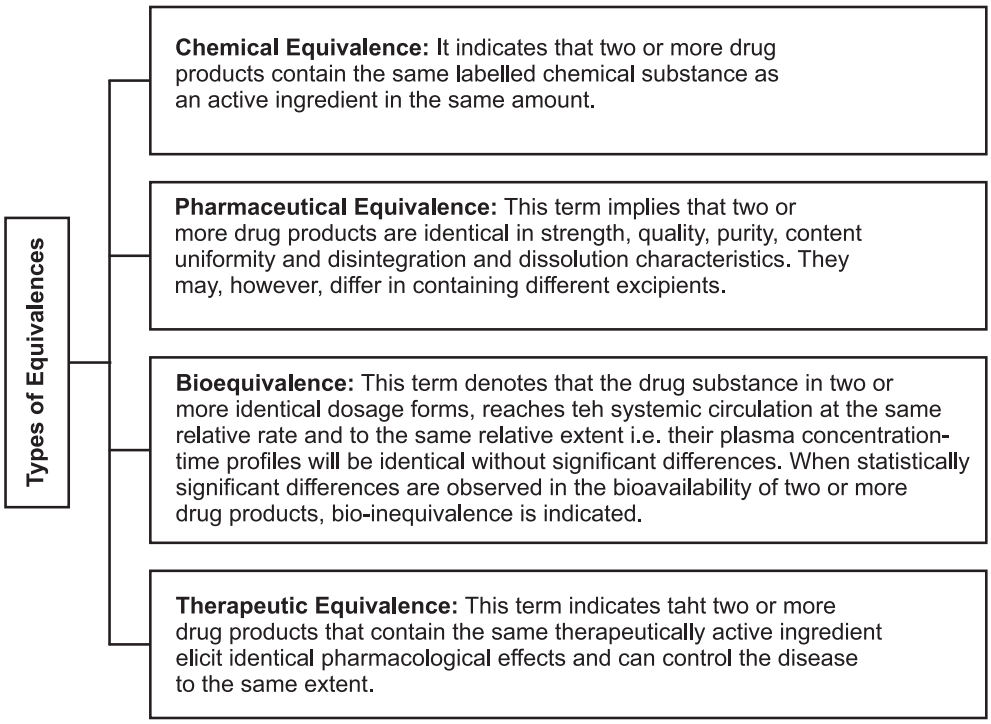

Fig. 3.13: Types of Equivalences

3.17 CLINICAL RESEARCH PROTOCOLS

- It is a complete written description of and scientific rationale for a research activity involving human subjects.
- Sufficient information is to be gathered on the quality of the non-clinical safety to conduct the protocol and health authority/ethics committee approval is granted in the country where approval of the drug or device is sought.

- The clinical trial design and objectives are written into a document called a clinical trial protocol. It is a document that states the background, objectives, rationale, design, methodology (including the methods for dealing with AEs, withdrawals etc.) and statistical considerations of the study. It also states the conditions under which the study shall be performed and managed.
- Look for better ways to prevent disease in people who never had the disease or to prevent a disease from returning.
- The protocols means:
  - To clarify the research question.
  - To compile existing knowledge.
  - To formulate a hypothesis and objectives.
  - To decide about a study design.
  - To clarify ethical considerations.
  - To apply for funding.
  - To have a guideline and tool for the research team.

Parts of the Protocol:

1. Title Page.
2. Signature Page.
3. Content Page.
4. List of Abbreviations.
5. Introduction/Abstract.
6. Objectives.
7. Background/Rationale.
8. Eligibility Criteria.
9. Study Design/Methods (Including Drug/Device Info).
10. Safety/Adverse Events.
11. Regulatory Guidance.
12. Statistical Section (Including Analysis and Monitoring).
13. Human Subjects Protection/Informed Consent.

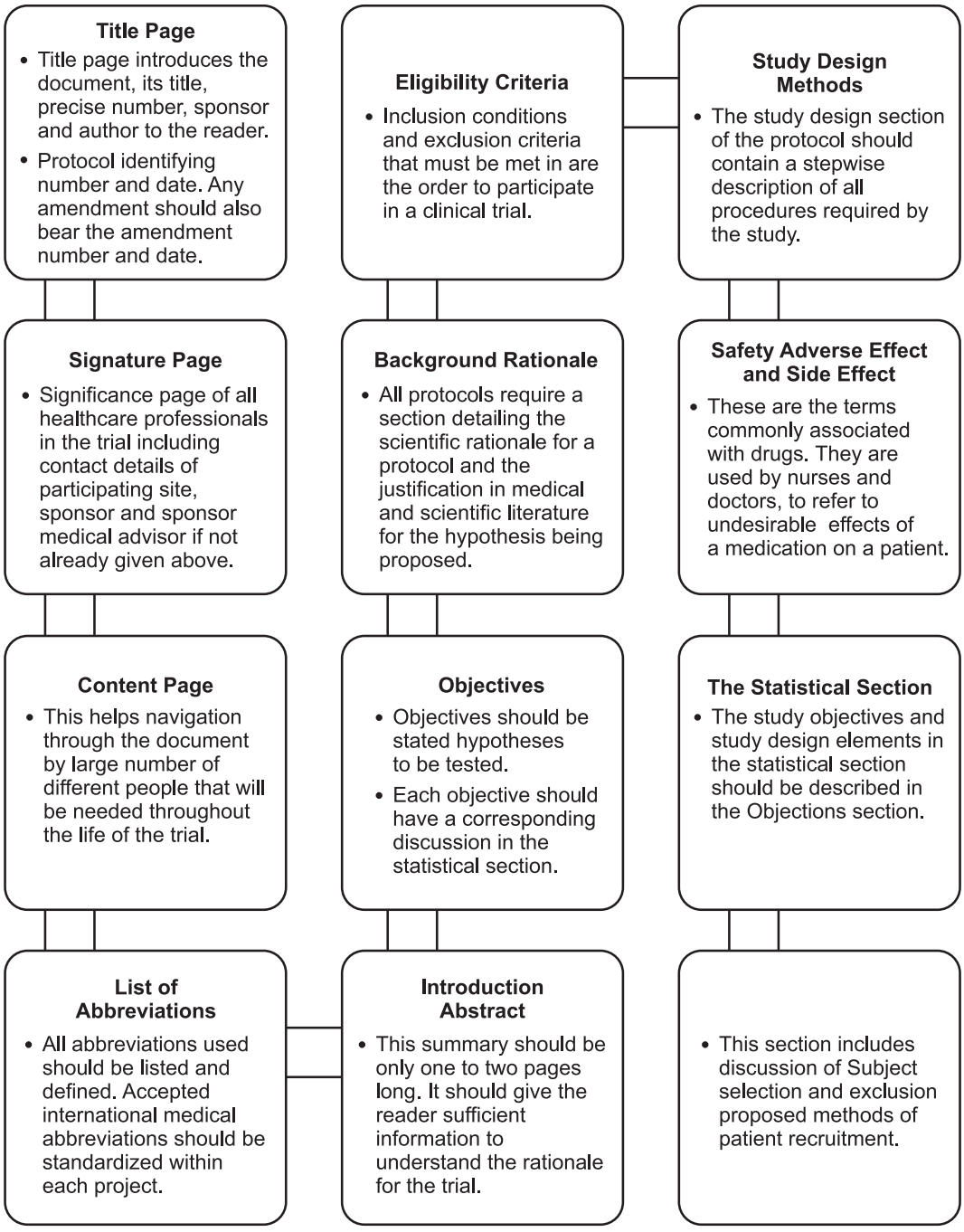
Title Page
• Title page introduces the document, its title, precise number, sponsor and author to the reader.
• Protocol identifying number and date. Any amendment should also bear the amendment number and date.
Eligibility Criteria
• Inclusion conditions and exclusion criteria that must be met in are the order to participate in a clinical trial.
Study Design Methods
• The study design section of the protocol should contain a stepwise description of all procedures required by the study.
Signature Page
• Significance page of all healthcare professionals in the trial including contact details of participating site, sponsor and sponsor medical advisor if not already given above.
Background Rationale
• All protocols require a section detailing the scientific rationale for a protocol and the justification in medical and scientific literature for the hypothesis being proposed.
Safety Adverse Effect and Side Effect
• These are the terms commonly associated with drugs. They are used by nurses and doctors, to refer to undesirable effects of a medication on a patient.
Content Page
• This helps navigation through the document by large number of different people that will be needed throughout the life of the trial.
Objectives
• Objectives should be stated hypotheses to be tested.
• Each objective should have a corresponding discussion in the statistical section.
The Statistical Section
• The study objectives and study design elements in the statistical section should be described in the Objections section.
List of Abbreviations
• All abbreviations used should be listed and defined. Accepted international medical abbreviations should be standardized within each project.
Introduction Abstract
• This summary should be only one to two pages long. It should give the reader sufficient information to understand the rationale for the trial.
• This section includes discussion of Subject selection and exclusion proposed methods of patient recruitment.

Fig. 3.14

3.18 DATA PRESENTATION FOR FDA SUBMISSIONS

Study data standards describe a standard way to exchange clinical and non-clinical study data. These standards provide a consistent general framework for organizing study data, including templates for datasets, standard names for variables; identify appropriate controlled terminology and standard ways of doing calculations with common variables. Data standards also help FDA receive, process, review, and archive submissions more efficiently and effectively.

- FDA has been working towards a standardized approach to capture, receive and analyze study data.
- Standardization of study data is vital to integrate pre-marketing study data and post-marketing safety data to improve public health and patient safety.
- Central to this vision is the creation of an enterprise data infrastructure (Janus) within FDA to improve the management of all structured scientific data.

Data Standards: Data standards can be divided into two categories:

1. **Exchange Standards:** Exchange standards provide a consistent way to exchange information. Exchange standards help to ensure that the sending and the receiving systems both understand unambiguously what information is being exchanged.
2. **Terminology Standards:** Terminology standards provide a consistent way to describe concepts. For example, the Unique Ingredient Identifiers (UNII), developed by the FDA, provides a consistent way to describe substances in foods and drugs. Vocabulary developed National Institute of Cancer describes terminology related to cancer.

3.19 MANAGEMENT OF CLINICAL STUDIES

Clinical trial management is most simply defined as the process that an organization follows to ensure that quality (defined as minimized risks and clean data) is delivered efficiently and punctually. It refers to a standards-driven process that a project manager initiates and follows in order to successfully manage clinical trial sites, clinical research associates, and workflow by using clinical trial management tools or software prolonged timelines and heavy costs related to large trials have been prompted a new focus on more efficient clinical trial management. It is possible to dramatically reduce the total cost of a clinical trial by 60% - 90% without compromising the scientific validity of the results.

Life Cycle of Clinical Trial Project: A more accurate control, regardless of the therapeutic area or trial stages (all the way through from 'preclinical' phase 1 to 'post-approval' phase 4 studies), is ensured by typically breaking down the life cycle of each clinical trial project into 4 phases: Conceptual, Planning, Implementation and Analysis.

Clinical Trial Protocol: A protocol is a document that describes the purpose, design, methodology, statistical considerations and organization of a study, and provides basic information and rationale for the clinical study. The contents that should be present in the protocol are described by the GCP. The protocol writing is a task for one person, usually the principal investigator, not a committee.

There are various challenges of Project management in clinical trials. Clinical trials all need the same coordinated processes and systems, irrespective of the size, scope, costs, or period. The key challenge is then to implement and maintain effective management systems and techniques in response to the needs of the trial project.

QUESTIONS

Multiple Choice Questions:

1. Who are the study leaders based at each site during the clinical trial?
   (a) Chief medical officer and clinical research associates.
   (b) Principal investigators and study coordinates
   (c) Study coordinates and chief medical officer
   (d) Principal investigators and clinical research associates.
2. What is the purpose of the case report form?
   (a) To ensure data accuracy by providing a place to store warehouse patient data for audit purposes.
   (b) To provide a reference for all study subjects from which to analyze patient data.
   (c) To include in the NDA filing.
   (d) All of above.

3. At the end of the study, what happens to the case report forms (CRFs)?
   (a) The CRF data is compiled and submitted to the FDA in the IND.
   (b) The CRF data is aggregated by an external party if the trial was double blinded to assess the drug's safety and efficacy.
   (c) The CRF data is aggregated and analyzed to assess the drug's safety and efficacy.
   (d) The CRF data is compiled and submitted to Regulatory Affairs
4. What is the primary focus of Phase 3 Clinical testing?
   (a) How to manage costs.
   (b) The collection and analysis of highly specific efficacy end-point data
   (c) The optimal range of effective dosage.
   (d) The analysis of data results from the small-subset target population
5. On which two criteria does the FDA classify NDAs?
   (a) Novelty of the active ingredient and time to market
   (b) Balance between safety and effectiveness
   (c) Novelty of the active ingredient and clinical improvement
   (d) Clinical improvement and effectiveness of product

ANSWERS

1. (b)	2. (d)	3. (c)	4. (b)	5. (c)

Long-Answer Questions:

1. What is an NDA? Discuss the requirements of data while filing a NDA. Give examples where a NDA can be filed.
2. Comment on the bioequivalence requirements according to ICH guidelines.
3. Discuss the Intellectual Property protection laws in India in brief.
4. What is PCT? Discuss the content of PCT and its applications.
5. Write a note on Drug Master Files.
6. Briefly discuss Master Formula Record and its importance.

7. What are the elements of a clinical trial? Describe systematically the protocol of a clinical trial.
8. Write short notes on Pharmacovigilance.
9. Write short notes on Investigator Brochure.
10. Discuss the NDA regulatory approval process with suitable example.
11. Write a note on outsourcing BA-BE studies to CRO.
12. Write short notes on the Post marketing surveillance.

***

Chapter ... 4

QUALITY MANAGEMENT SYSTEMS

♦ **LEARNING OBJECTIVES** ♦

After completing this chapter, students will be able to understand:

- ❖ Quality concepts in pharmaceutical industry
- ❖ ICH guidelines and Total quality management
- ❖ Quality by design and six sigma concepts
- ❖ ISO standards and series
- ❖ Good laboratory practice

4.1 QUALITY MANAGEMENT SYSTEM: CONCEPT OF QUALITY

4.1.1 Introduction

Quality Management System (QMS) is an important aspect for the pharmaceutical industry for maintaining the quality and safety for their products and services. QMS relies on the regulations and guidelines to maintain the effective quality in pharmaceutical industries. According to US FDA, the international harmonized guidance is intended to assist pharmaceutical manufacturers by describing a model for an effective quality management system for the pharmaceutical industry. This guidance is referred as ICH (International Council for Harmonization) guideline.

4.1.2 Quality

Quality can be defined according to US FDA as; "A measure of a product's or service's ability to satisfy the customer's stated or implied needs."

4.1.3 Quality in Pharma Industry

Due to the effect of globalization, market competition, cost constrains, supply and demand, complexity of supply chain system and development of international guidelines and regulations, the environment of pharmaceutical industry is changing day by day. The quality, safety and efficacy cannot be ignored or compromised as pharma-industry is directly concerned with the patients to provide them zero defect products.

4.1.4 Quality Assurance (QA)

According to WHO, "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

4.1.5 Quality Control (QC)

QC is that part of GMP concerned with sampling, specification, testing, documentation and release procedures which ensure that the necessary and relevant tests are performed and the product is released for use only after ascertaining its quality.

4.1.6 Scope of Pharmaceutical QMS

According to US FDA, pharmaceutical QMS is applied to the development and manufacture of pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle. For the purpose of this guidance, the following technical activities can be included:

Pharmaceutical Development:

- Drug substance development.
- Formulation development (including container/closure system).
- Manufacture of investigational products.
- Delivery system development (where relevant).
- Manufacturing process development and scale-up.
- Analytical method development.

Technology Transfer:

- New product transfers during development through manufacturing.
- Transfers within or between manufacturing and testing sites for marketed products.

Commercial Manufacturing:

- Acquisition and control of materials.
- Provision of facilities, utilities and equipment.
- Production (including packaging and labeling).
- Quality control and assurance.

4.1.7 ICH Guidelines

ICH guideline is intended for bringing together the regulatory authorities and pharmaceutical industries together for the discussion of the scientific and technical aspects of drug registration.

It is divided into four categories (QSEM):

Q: Quality guidelines - It includes stability, impurities testing, GMP.

S: Safety guidelines - It includes carcinogenicity, genotoxicity, reprotoxicity.

E: Efficacy guidelines - It includes clinical, pharmacogenomics.

M: Multidisciplinary guidelines - It includes medical dictionary for regulatory activities, electronic standards, non-clinical safety studies, common technical document (CTD).

1. Quality Guidelines:

Harmonization achievements in the quality area include pivotal milestones such as the conduct of stability studies defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quantity based on good manufacturing practice (GMP) risk management.

It includes the following guidelines:

Q1 (A-F): Stability
Q2: Analytical validation
Q3 (A-D): Impurities
Q4 (A-B): Pharmacopoeias
Q5 (A-E): Quality of biotechnological products
Q6 (A-B): Specifications (Test procedures and acceptance criteria for new drug substances and biological products)
Q7: Good Manufacturing Practice
Q8: Pharmaceutical development
Q9: Quality Risk Management
Q10: Pharmaceutical Quality System
Q11: Development and manufacture of drug substances
Q12: Lifecycle management
Q13: Continuous manufacturing of drug substances and drug products
Q14: Analytical process development

2. Safety Guidelines:

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity.

S1 (A-C): Carcinogenicity studies
S2: Genotoxicity studies
S3 (A-B): Toxicokinetics and Pharmacokinetics
S4: Toxicity Testing
S5: Reproductive Toxicology
S6: Biotechnological Products
S7 (A-B): Pharmacology Studies
S8: Immunotoxicology studies
S9: Non-clinical evaluation for Anticancer Pharmaceuticals
S10: Photosafety evaluation
S11: Non-clinical pediatric safety
S12: Non-clinical bio-distribution Studies for Gene Therapy Products

3. Efficacy guidelines:

It is concerned with the design, conduct, safety and reporting of clinical trials.

E1: Clinical Safety for Drugs used in Long Term Treatment
E2 (A-F): Pharmacovigilance
E3: Clinical Study Reports
E4: Dose-Response Studies
E5: Ethnic Factors (in the Acceptability of Foreign Clinical Data)
E6: Good Clinical Practice
E7: Clinical Trials in Geriatric Population
E8: General Considerations for Clinical Trials
E9: Statistical Principles for Clinical Trials
E10: Choice of Control group in Clinical Trials
E11: Clinical Trials in Pediatric Population
E12: Clinical Evaluation by Therapeutic Category
E14: Clinical evaluation
E15: Definitions in Pharmacogenetics
E16: Qualification in Genomic Biomarkers
E17: Multi-Regional Clinical Trials
E18: Genomic Sampling
E19: Safety Data Collection
E20: Adaptive Clinical Trials

4. Multidisciplinary Guidelines:

Some highlights of this guideline are:

M1: ICH medical terminology
M2: Electronic Standards
M3: Nonclinical Safety Studies
M4: Common Technical Document-CTD
M6: Gene Therapy
M7: Mutagenic impurities
M10: Bioanalytical Method Validation
M12: Drug Interaction Studies

4.1.8 Sources of Quality Variation

1. Materials:

(a) Variations among suppliers of same substances.
(b) Variations among batches from same suppliers.
(c) Variations within a batch.

2. Machines:

(a) Variation of equipment of same process.
(b) Difference in adjustments of equipment.
(c) Aging of machines and improper care.

3. Methods:

(a) Wrong procedure.
(b) Inadequate procedure.
(c) Negligence in procedure by chance.

4. **Personnel:**
   (a) Improper working conditions.
   (b) Inadequate training and understanding.
   (c) Lack of interest and emotional upheavals.
   (d) Dishonesty fatigue and carelessness.

4.1.9 Control of Quality Variation

The mistakes can be controlled, minimized or eliminated by material control; packaging control and GMP variations can be controlled when Quality Control, Quality Function, and Quality Assurance work side by side.

Controlling each and every step of process can control variations. Control can be divided into:

1. Material control
2. Manufacturing practice control
3. Packaging control
4. Distribution control

4.2 TOTAL QUALITY MANAGEMENT

4.2.1 Introduction

The pharmaceutical industry is key part of the health care system. The regulation of this industry is very important because one mistake in production or design can cause more severe condition in relation to health care system. So, the maintenance of the quality of the drugs is so important in pharmaceutical industries because the poor quality of drugs can cause health hazards and economical burden for both the government and patients. Total quality management is improvised in the industries to maintain the quality and safety of the drugs and prevention of the defects rather than the detection. The pharmaceutical quality system is described under ICH guideline Q10. The concepts, key points of quality improvement of TQM were proposed by several eminents like Edward Deming, Joseph Juran, Philip Crosby, Genichi Taguchi, etc.

4.2.2 Definition

As per International Organization of Standard (ISO), TQM is defined as: "A management approach of an organization centered on quality, based on participation of all its members and aiming at long term benefits to all members of the organization and society".

4.2.3 Focus of TQM

There are three main key components of TQM:

1. Consumer/Customer focus
2. Involvement of employee
3. Continuous improvement

TQM is controlled by customer focus, process (planning, management and improvement) and total participations. According to previous literature (Mazumder et al, 2011), the key ingredients of TQM are:

1. Strategic commitment by the management
2. Employee involvement
3. Materials used in the organizations
4. Precise techniques used by the organizations and
5. Improved methods

4.2.4 Statistical Quality Control

To achieve accuracy, statistics play an important role in quality management systems. The seven major tools used for statistical process control are:

1. **Histogram:** A histogram is an accurate representation of the distribution of numerical data (related with one variable).
2. **Pareto chart:** A Pareto chart is a type of chart that contains both bars and a line graph, where individual values are represented in descending order by bars, and the cumulative total is represented by the line.
3. **Cause and effect diagram (Fish bone diagram):** It helps to identify the possible causes of a specific problem or quality characteristic.

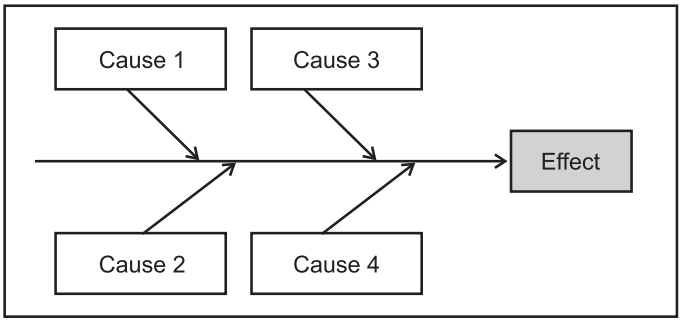

Fig 4.1: Cause and effect diagram

4. **Defect concentration diagram.**
5. **Control chart:** The control chart is a graph used to study how a process changes over time. Data are plotted in time order. A control chart always has a central line for the average, an upper line for the upper control limit and a lower line for the lower control limit.
6. **Scatter diagram:** The scatter diagram graphs pairs of numerical data, with one variable on each axis, to look for a relationship between them. If the variables are correlated, the points will fall along a line or curve.
7. **Check sheet:** The check sheet is a form or document used to collect data in real time at the location where the data is generated.

4.2.5 Advantages

1. Improve in quality and safety of the drugs.
2. Improvement of customer satisfaction.
3. Improvement of reputation of industry.
4. Total involvement of employee with higher moral and responsibilities.
5. Lower economic burden.

4.3 QUALITY BY DESIGN (QbD)

4.3.1 Introduction

Pharmaceutical industries always rely on the continuous improvement in safety, quality and efficacy of the products. The pharmaceutical products are intended for the patient care. So, the priority is enhanced therapeutic benefits and absence of impurities. Therefore, the product should be designed to meet patients' needs and the intended product performance. The product quality and performance are regulated by finished product testing, with understanding of the process and critical process parameters. The US FDA (Food and Drug Administration) has adopted the principles of QbD in the development, manufacturing and regulation of pharmaceutical products. ICH guidelines also focus on the principles of QbD through its guidelines mentioned as ICH Q8 (R2)- Pharmaceutical Development, ICH Q9 (Quality Risk Management), ICH Q10 (Pharmaceutical Quality System) and ICH Q11 (Development and manufacture of drug substances).

4.3.2 Definition

According to US FDA and ICH Q8 (R2) the QbD is a systematic approach to development which includes the prior knowledge of product and process understanding based on the results of studies using design of experiments, use of quality risk management and use of knowledge management.

4.3.3 Objectives of QbD

The main objectives of QbD are as follows:

1. Increasing manufacturing efficiency.
2. Increasing the efficiency in product development.
3. Enhancement of product quality and performances to meet patients' needs.
4. Increase in process capability.
5. Avoidance of regulatory compliances.
6. Incorporation of risk management.
7. Reduction in production costs and waste.
8. Reduction in product variability, defects and rejections.

The main outcomes of QbD are as follows:

1. Maintenance of product quality to meet expected clinical performances.
2. Maintenance of product quality by efficient manufacturing and formulation process.

4.3.4 Elements of QbD

The following elements can be included in the study of QbD:

1. **QTPP (Quality Target Product Profile):** This profile is related to quality, safety and efficacy.
2. **CQAs (Critical Quality Attributes):** The study of CQAs helps in the study and controlling of the product characteristics that have impact on product quality.
3. **Determination of CQAs** of drug substances, excipients, etc. and the selection of the excipients to attain the desired drug quality.
4. **Suitable manufacturing process selection.**
5. **Risk assessment:**
   - CMAs (Critical Material Attributes)
   - CPPs (Critical Process Parameters)
6. **Defining a control strategy.**

4.3.5 Quality Target Product Profile (QTPP)

It includes:

1. Dosage forms, route of administration, delivery systems.
2. Strength of doses.
3. Container closure system.
4. Pharmacokinetic properties.
5. Drug product quality criteria.

4.3.6 Critical Quality Attributes (CQA)

CQA is related with drug substance, excipients, intermediates (in-process materials) and drug product. CQA is a physical, chemical, biological or microbiological property (should be within an appropriate limit, range, or distribution) to ensure the desired product quality.

4.3.7 Risk Assessment: CMAs (Critical Material Attributes) and CPPs (Critical Process Parameters)

Risk assessment, a science-based method or process, is used in QRM (Quality Risk Management, mentioned in ICH Q9). This assessment identifies materials attributes and process parameters effectively that have an effect on product CQAs. This process is utilized in prior pharmaceutical development process which makes available more information and knowledge about the development process. Based on prior knowledge and initial experimental data, risk assessment method helps to identify and rank different parameters like process, equipments and input materials with potential that have an impact on product quality.

4.3.8 Control Strategy

The pharmaceutical product should be produced with required quality in consistent fashion and the control strategy ensures this. It includes the following elements:

1. Control of input material attributes *viz.,* drug substance, excipients, packaging materials, considering their utilization and effect on product quality.
2. Product specifications.
3. Controls of unit operations that have a role to maintain the product quality. The operations may include granulation, drying, degradation, particle size distribution, etc.
4. In-process testing.
5. Finished product testing.
6. Testing of products at every stage at regular intervals (Monitoring program).

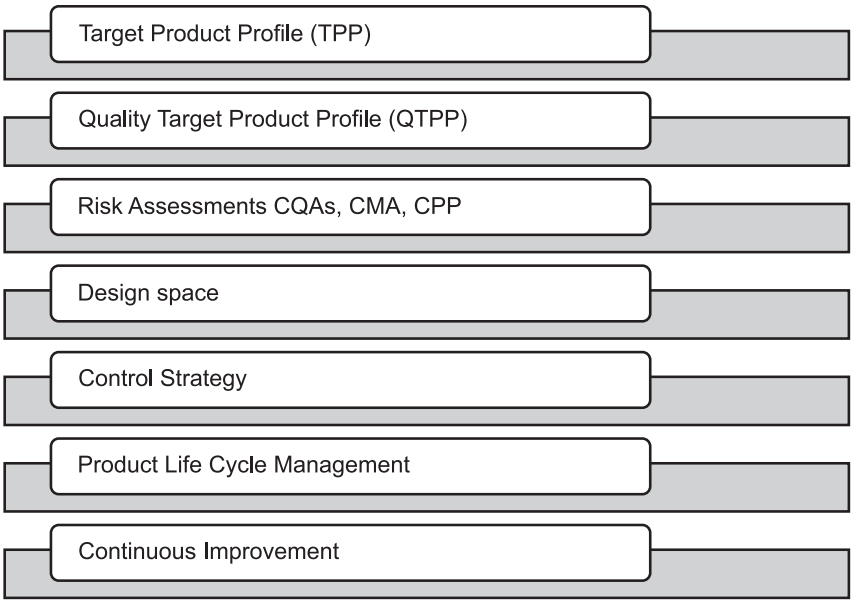

Fig. 4.2: Quality by Design (QbD)

4.4 SIX SIGMA CONCEPTS

4.4.1 Introduction

Six sigma concepts are a principle for the process improvement. Six sigma represents the quality level which is implemented for reducing the operational costs in pharmaceutical industry and serving the best customer satisfaction and services. Six sigma is symbolized as "6σ". Six sigma is a statistical measurement of product variables. This concept helps to achieve stable and predictable process results with continuous quality improvement.

4.4.2 Aim of Six Sigma Concept

The main aims of the six sigma concept are as follows:

1. Process improvement
2. Improved methodology
3. Improved quality
4. Customer satisfaction

5. Reduction in process variation
6. Reduction in costs
7. Fewer defects to achieve the goal
8. Continuous quality improvement

4.4.3 Six Sigma Process

The concept is designed in "DMAIC" process. DMAIC stands for Define, Measure, Analyze, Improve and Control.

1. **Define: '**Define' is the first and more difficult step of six sigma approach. The basic aim of this step is defining the problems and objectives. 'Define' explains project goal, aim, difficulties, target magnitude and time span to achieve the improved process.
2. **Measure:** This is the process of collecting expected future data. The data will help to understand the magnitude of improvement and will answer either the expected improvement can be measured or not. The data is not necessarily quantitative.
3. **Analyze:** This process includes the analysis of the whole process and helps to understand the factors of influence. This is nothing but the analysis of raw data to establish a correlation between input variables and the possible output that implies critical quality attributes (CQAs).
4. **Improve:** The next step is improvement of the process that has been outlined in the define step to achieve the expected outcome and result. The principles, specifications and process outflow selected in the first step should be improved and incorporated in the lifecycle with fewer defects.
5. **Control:** The improvement done in the last step should be retained and additional procedures may be included in the workflow.

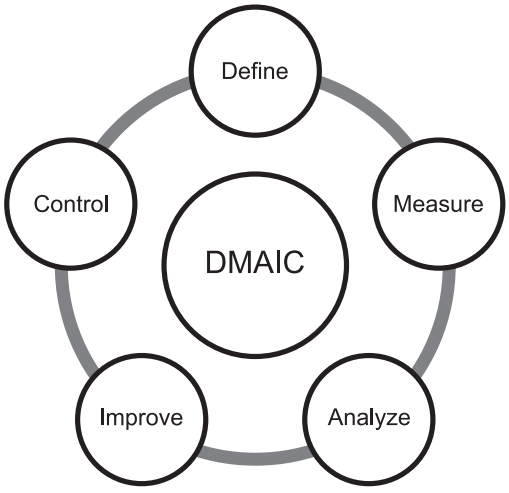

Fig. 4.3: Six Sigma Concept: DMAIC

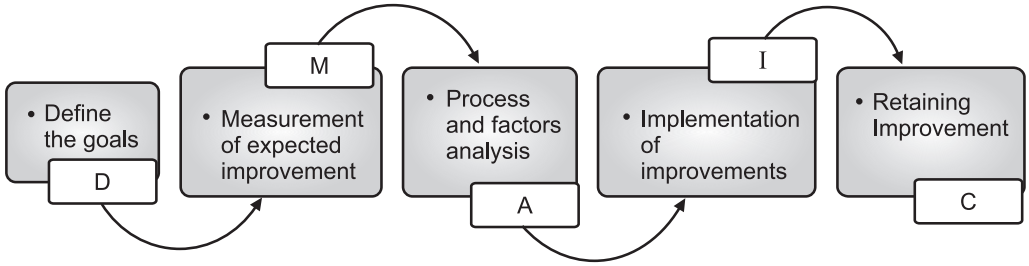

Fig. 4.4: Six Sigma Process: DMAIC

4.5 OUT OF SPECIFICATIONS (OOS)

4.5.1 Introduction

When an analytical or test result of any batch or material is out of prescribed and predetermined limits or specifications, it is called as OOS. OOS may be raised in the case of stability testing, analysis of in-process, test of raw materials, intermediates and finished goods (API). Investigation for OOS may be performed while getting any unacceptable and questionable results.

4.5.2 Identification of OOS: Reports of Laboratory Investigation

This investigation is conducted when OOS is found in analysis. The main purpose of obtaining OOS reports is to find out the source of the results which fall outside the specifications. In this initial investigation, all the results should be recorded and well documented. The data should be conveyed and forwarded to quality control department, so that full scale analysis can be performed.

4.5.2.1 Responsibility of Analyst and Supervisor

An analyst has the primary responsibility for the laboratory testing results. He should have sound knowledge about the principle, primary requirements and process of the investigations. The accurate and precise results are expected, if any wrong results are found that should be informed to concern superior department and assessment should be initiated with immediate effect. The supervisor of the laboratory should discuss the problems and the malfunctioned result with the analyst. He should verify the followed correct procedure and knowledge of the analyst. He should overlook the following points:

1. Raw data of the result.
2. Calculations of the result.
3. Proper functioning of instruments.
4. Procedure performed by the analyst.
5. Quality parameters of solvents, reagents, standard solutions.
6. Knowledge of the analyst regarding investigation.
7. Method validation and evaluation of performance.
8. Preservation of the results obtained.

4.5.3 Identification of OOS: Reports of Full-Scale Investigation

When an initial analysis does not confirm the errors caused by OOS result from lab investigations, full scale investigations with proper design should be performed. The identification of the source of the errors and the action taken for the correctness are the main objectives of this investigation. The following are the important aspects of OOS results identification with respect to full scale investigation.

1. Review of manufacturing, production and sampling.
2. Review of lab investigation result.
3. Supplementary laboratory testing procedure.

4.5.3.1 Review of Manufacturing, Production and Sampling

To find out the OOS results, review of manufacturing, production and sampling is very important. The errors and problems should be investigated and identified. The documents and records of manufacturing and production should be reviewed. The investigations should be reviewed through a well-documented manner.

4.5.3.2 Review of Lab Investigation Result

It contains the following information:

- Cause of the investigation.
- Review and summary of manufacturing process (which may have identified as malfunctioned or cause of OOS results).
- Review of previous results to find out the possible causes of OOS results.
- Review of documented records to analyze the possible factors of wrong results.
- The actions taken to correct the process.

4.5.3.3 Supplementary Laboratory Testing Procedure

To investigate OOS results in full scale, additional laboratory testing may be performed. This includes Re-testing and Re-sampling.

In Re-testing, a portion of original samples are tested again according to the standard procedures. The results are kept in a well documented manner. This process helps to find out the problems encountered due to error in instruments, process, dilution or sample handling.

In Re-sampling, a specimen is collected from any additional units from original sample or a new sample is prepared from the same batch and analyzed further.

4.5.4 Analysis of Investigated Results

The reported results should be analyzed and interpreted to find out the possible, probable and actual causes of OOS results. Some possibilities are discussed below:

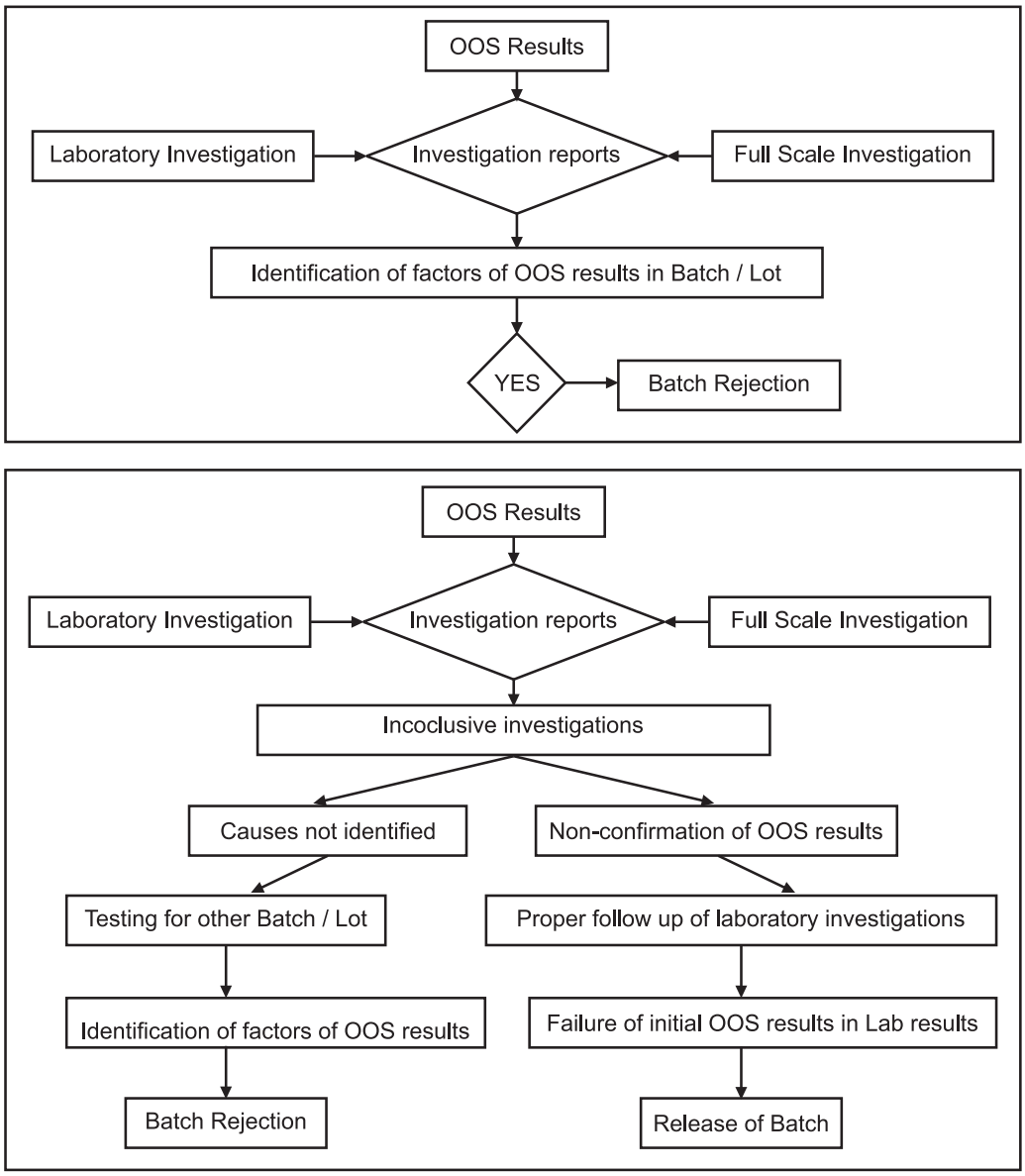

Fig. 4.5: Analysis of investigated results

4.6 CHANGE CONTROL

4.6.1 Introduction

In pharmaceutical industry change control is an important part of quality assurance. The changes proposed and made in any procedure or process should be reviewed, established, documented and approved by the concerned authorities. Change control is the system to implement this approved change to confirm the regulatory requirements.

4.6.2 Definition

Change control can be defined as; "A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state". (EU GMP Guidelines, Annexure 15).

4.6.3 Function

Any change in manufacturing process, equipment, materials used that may cause alteration in product quality should be validated.

The main functions of change control are:

1. Identification of the changes made.
2. Review of the change.
3. Approval of the change.
4. Validating the changes which can alter the product quality, regulatory or GMP (Good manufacturing process) requirements.
5. Analysis of the change and monitoring of the impact of change.

4.6.4 Area of Change

1. **Manufacture:** Following changes are concerned:
   - Raw materials
   - Equipments
   - Process/parameters
   - Testing/validation procedures
   - Packaging materials
   - Cleaning process
2. **Quality control and quality assurance:** Following changes are considered:
   - Quality testing parameters
   - Sampling size
   - Validation process
   - Specifications of raw materials, intermediates and final product
   - Documentation
   - Standard operating procedures (SOPs)
3. **Research and development:** It includes the change in;
   - Manufacturing process (any addition of elimination of steps)
   - Raw materials (any addition of omission of the product)
   - Specifications of raw materials, intermediates and final product
   - Quantitative aspects of raw materials and finished products
   - Manufacturing conditions and storage conditions
   - Testing/validation procedures

4. **Engineering:** It includes the following changes in:
   - Equipment used
   - Validation of the equipment
   - Parts of equipment
   - Working and design layout
   - Software/ Hardware or Change in any program
5. **Marketing.**

4.6.5 Written Procedures and Documentation

Procedures in writing should be kept at the proper place to describe the changes made related to the materials, equipment and method of manufacturing or testing conditions or any other change that can affect the quality of the product. Standard operating procedure (SOP) and records of change control documents are required for the documentation. The Change Control Form (CCF) is an important documentation part of change control. It contains the form related to initiate department for the proposed change, proposed change details, comments from QA Head, category of the changes, supportive documents, management review form and assessment of CCF.

Table 4.1: Change control log book

Change control (CC) No.	Initiated Department	Originator Name	Proposed Change	Category of change	Approval/ Rejection of CC	Date of Change	Verified by QA Head (Sign and Date)	Any remark

4.7 ISO QUALITY STANDARDS

4.7.1 Quality Management System (QMS)

The quality policy and objectives of any organization are implemented, defined and established by QMS. QMS allows documenting and implementing the procedures for an organization to attain the goals. The procedures should be carried out consistently, related problems should be identified and dissolved, and continuous improvement in the procedures through extensive reviews should be done to improve the quality of the products and service. Proper implementation of QMS will ensure the better service and customers' satisfaction.

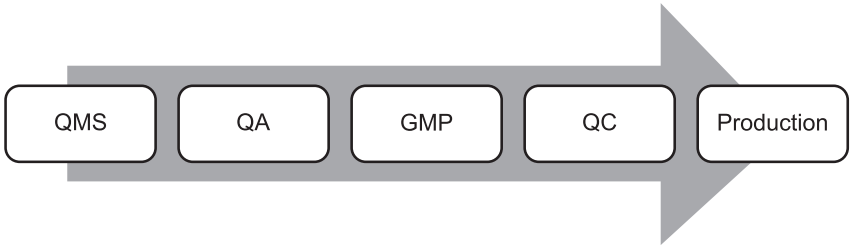

Fig. 4.6: Relationship among QMS, QA, GMP and QC

4.7.2 ISO Quality Standards

International Organization for Standardization (ISO) is an international standard of QMS. This written international standard is implemented by ISO. It is an independent organization with more than 150 national standard bodies.

To serve the satisfaction to the customers, an organization needs standards through QMS and ISO. The needs of standard are for the following points:

- For customer satisfaction and safety, which depend on output of the organization.
- For maintaining the quality system that is auditable and verifiable with continuous mode.
- For the continuous improvement and effectiveness of the organization with main focus on customer.

ISO standard is concerned with the

- Standard development based on global expert opinion.
- Capacity building activities by technical assistance.
- Research and training for the education about standards.

The history of ISO though began in 1946, in 1947 ISO started officially its operation and in 1951 the first ISO standard was published.

4.7.3 ISO 9000

The ISO 9000 family of standards is designed to help organizations to ensure the customers' needs, the statutory and regulatory requirements. It does not certify any organization. It certifies the QMS of any organization. The basic quality management principles (QMP) of ISO 9000 are:

QMP 1: Customer focus
QMP 2: Leadership
QMP 3: Engagement of people
QMP 4: Process approach
QMP 5: Improvement
QMP 6: Evidence based decision making
QMP 7: Relationship management

4.7.4 ISO 9000 Series

ISO 9000: Quality assurance and quality management concepts, guidelines for selection and use.

ISO 9001: Concepts for QA in design, production and development of the system, along with service and installation.

ISO 9002: Concepts for QA in production, service and installation.

ISO 9003: Model for QA in final inspection and finished good testing.

ISO 9004: Guidelines for quality assurance and quality management planning, implementation, efficiency and improvement.

4.7.5 Requirements of ISO 9000 Series

To establish an effective QMS through ISO 9000 series the following points are necessary:

1. **Responsibility of the Management of the Organization:** The policy to maintain the quality should be ensured by the management of the organization. The quality policy should be implemented and maintained in all the spheres of the organization.
2. **Quality System and Design Control:** The supplier of raw materials should maintain the quality and documents regarding specifications of the materials. The products should meet predetermined quality and standards.
3. **Documentation regarding Stakeholder's Contract and Purchasing:** The well documented contract review with different suppliers should be maintained by the management. The capability of the contractor should be defined and documented. The details of purchasing and all data should be in documentation and maintained for the record to attain the desired quality management in the organization.
4. **Process Control:** The design of work flow should be decided, planned, defined and implemented. The responsibilities should be defined to the personnel for the equipment, process and the change if any in the protocols that should be well documented, reviewed and proposed for the prior approval from the higher and concerned authorities. The production plan, installation and service should be finalized by keeping in mind that the variations in reaction condition shall alter the quality of the finished products. The inspection of validation of equipment, calibration process and efficiency are the important concerns.
5. **Final Inspection and Testing of Finished Goods:** The inspection and analysis for the finished products should be well documented and, test procedure and result should be reviewed and maintained for the record. The product that does not meet certain specifications should be prevented for the further process and installation.
6. **Actions taken to Overcome the Errors:** The possible causes for the errors should be identified and eliminated. The non-conformities of the products can affect the quality parameters and to maintain the quality management, the preventive actions should be taken, reported and documented. The implementations of the corrective measures should be confirmed.
7. **Internal Audits:** The effectiveness of the organization and system is determined by the quality internal audits. The audit report will assure the functioning of the system is adequate or not to maintain the desired quality of the products. The audit report shall be maintained and the corrective steps should be taken by the responsible individual in their respective areas if any deficiencies found. The audit in regular intervals assures the quality of the process in the organization.
8. **Training and Providing Education/Awareness regarding the Standards:** The personnel involved in the system shall be provided training, proper education or

workshops about the standards as per requirement. The training report shall be documented and maintained.

9. **Statistical Analysis:** To analyze and control the process capability, statistical analysis shall be documented and implemented.

4.7.6 Advantages of ISO Certification

1. Increment in marketability.
2. International recognitions.
3. Reliability in the market.
4. Capability of providing quality products to satisfy the customer.
5. Improvement in relationship with customers and stakeholders.

4.8 ISO 14000

4.8.1 Introduction

ISO 14000 family provides practical tools to manage the environmental responsibilities of companies and organizations. It was initially published in 1996 and revised in 2004. This standard is related to Environmental Management System (EMS). ISO 14000 is considered as generic management system and it is applicable for the following:

- Any organization (single-site to large MNCs, high risk to low risk companies).
- The manufacturing industries (equipment manufacturers and suppliers), process industries and service industries.
- All industries of local government, public and private sectors.

The basic features of ISO 14000 are:

- Minimum harmful effects on environment.
- Continuous improvement to achieve the desired performances.

4.8.2 Principle of ISO 14000

The principle of ISO 14000 is explained by PDCA Model.

1. **Plan:** Designing of aim, objective and processes to achieve the desired result.
2. **Do:** Designed process should be performed step by step. The changes are noted and data is stored to analyze the results.
3. **Check:** The evaluation of the data and results recorded in the previous steps.
4. **Act:** The evaluation of the data and results helps to improve the process. In this step, the problems of the result are rectified for the continuous improvement, for this purpose, Do and Check steps may be repeated several times for the better outcome. The causes of the difference in the results are identified and improved. This step is often named as 'Adjust'.

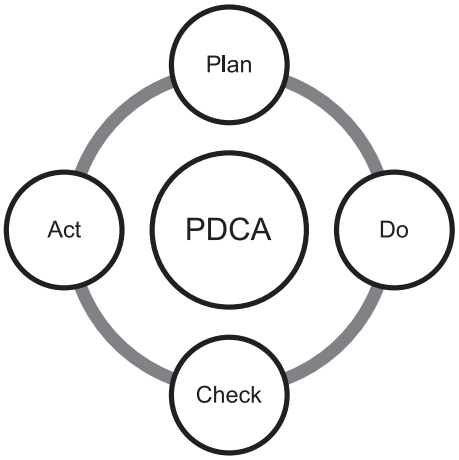

Fig. 4.7: PDCA Model

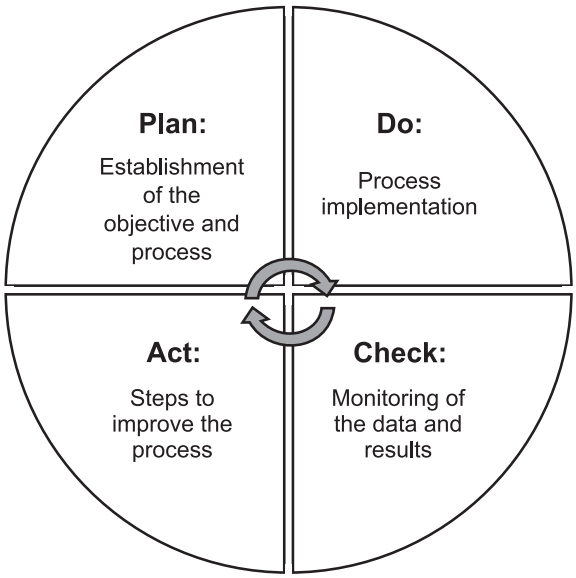

Fig. 4.8: Working of ISO 14000

4.8.3 Features of ISO 14000

The features of ISO 14000 are mentioned:

1. EMS (Environmental Management System).
2. Environmental related evaluations, investigations and auditing.
3. The investigation of the process performances.
4. Environmental labels and declarations.

4.8.4 Advantages of ISO 14000

By getting ISO certification any organization can maintain their conformation to the environmental regulations. This certification can help an organization by the following ways:

- Better marketability.
- Better utilization of resources.
- Environmental responsibilities.
- Better quality of finished goods and products.
- Customers' satisfaction.
- Enhancement of the reputation and reliability of the organization.
- Improvement of the relationship among management, employees, customers and investors.
- Reduction in cost.

4.8.5 ISO 14000 Series

- **ISO 14001 (2015)**
  EMS: Requirements with guidance for use
- **ISO 14004 (2016)**
  EMS*: General guidelines on implementation
- **ISO 14006 (2011)**
  EMS: Guidelines for incorporating ecodesign
- **ISO 14015 (2001)**
  EM#: Environmental assessment of sites and organizations (EASO)
- **ISO 14020 to 14025 (2000)**
  EM: Environmental labels and declarations
- **ISO 14031 (2013)**
  EM: Guidelines for environmental performance evaluation
- **ISO 14040 (2001)**
  EM: Life cycle assessment, environment goal setting
- **ISO 14050 (2009)**
  EM: Vocabulary (terms and definitions)
- **ISO 14063 (2006)**
  EM: Guidelines and examples of environmental communication
- **ISO 14064 (2006)**
  Quantification of emitted Greenhouse gases and their reduction

(**Note:** EM# and EMS* stand for Environment Management and Environment Management System respectively).

4.8.6 Process of ISO 14001 Certification

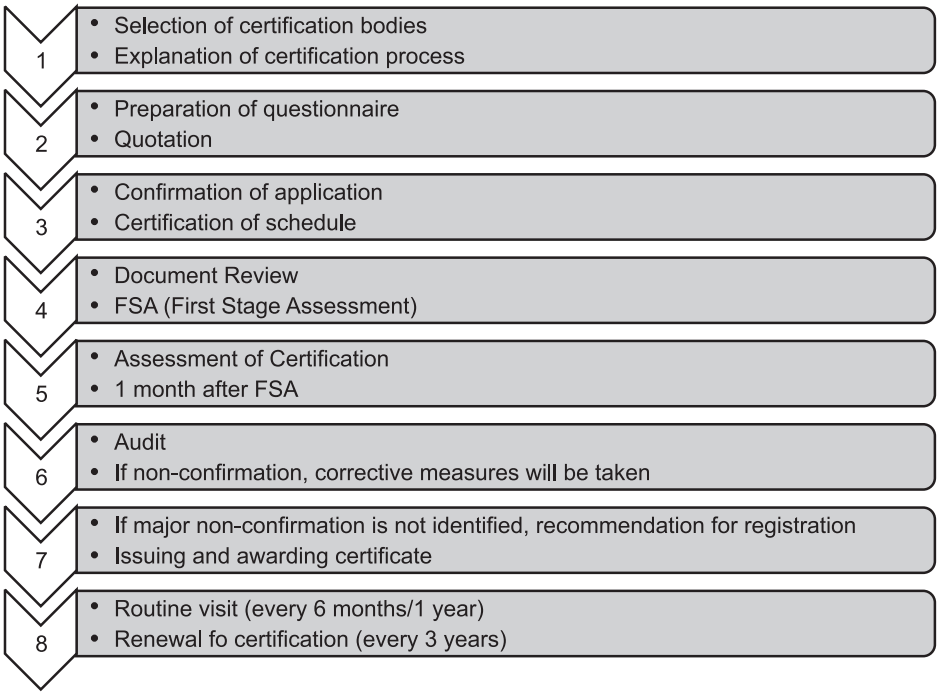

Fig. 4.9: Registration and Certification procedure of ISO 14001

4.8.7 Environmental Management System (EMS)

EMS is a system which monitors, reviews, summarizes, evaluates, reports and improves the environmental performances to achieve the environmental goal. EMS helps to reduce the environmental impact and to increase the efficiency. Waste reduction is one of the important goals of EMS.

4.8.8 Features of EMS

The EMS has the following features:

1. Improvement of environmental performances.
2. Controlling and managing of environmental policies in organization in systematic way to maintain the long-term effect of better products, service and customer satisfaction.
3. Process design to control the pollution and waste reduction.
4. Reducing the impact of environmental factors.
5. Training of the personnel about the process and control.
6. Assistance of planning, controlling and monitoring the environmental policies in organization.
7. Continuous improvement to meet the desired goal and result.
8. Maintains the accountability between the management and employee personnel.

4.9 NABL (NATIONAL ACCREDITATION BOARD FOR TESTING AND CALIBRATION LABORATORIES)

4.9.1 Introduction

NABL is an autonomous constituent board of quality council of India. NABL stands for "National Accreditation Board for Testing and Calibration Laboratories". NABL has been established and constituted for providing accreditation to the Government, industry associations and individual industry or organizations. The accreditation is related to the third-party assessment of the technical competence of testing which includes medical and calibration laboratories, proficiency testing providers (PTP) and reference material producers (RMP).

4.9.2 NABL and ISO Principles

The accreditation service is based on the following ISO principles:

1. **Accreditation Systems:**
   ISO/IEC 17011 (**2017**) (Conformity assessment-requirements for accreditation bodies accrediting conformity assessment bodies).
2. **Testing and Calibration Laboratories:**
   ISO/IEC 17025 (2005) and ISO/IEC 17025 (2017) (General requirements for the competence of testing and calibration laboratories).
3. **Medical Laboratories:**
   ISO 15189 (2012) (Medical laboratories-requirements for quality and competence).

4. **PTP (Proficiency Testing Providers):**
   SO/IEC 17043 (2010) (Conformity Assessment-General requirements for proficiency testing).
5. **RMP (Reference Material Producers):**
   ISO 17034 (2016) (General requirements for the competence of reference material producers).

4.9.3 Need of NABL

To achieve an international level acceptance for any laboratories, proficiency testing providers or RMPs, there is a need of a formal recognition to follow the international standards and acceptability to omit extensive re-testing. NABL is an authoritative body which provides the formal recognition for specific tests/ measurements by following international standards and third-party assessment.

4.9.4 Recognition of NABL in International Level

NABL maintains the relationship with several international bodies like:

1. International Laboratory Accreditation Co-operation (ILAC).
2. Asia Pacific Accreditation Co-operation (APAC).

4.9.5 Scope of NABL

In the following fields NABL accreditation is currently issued.

Table 4.2: NABL Accreditation

Testing Laboratories	• Biological • Chemical • Electrical • Electronics • Fluid-Flow • Mechanical • Non-Destructive Testing (NDT) • Photometry • Radiological • Forensic
Calibration Laboratories	• Electro-Technical • Mechanical • Fluid Flow • Thermal • Optical • Radiological • Medical Devices

Contd. …

Medical Laboratories	• Clinical Biochemistry • Clinical Pathology • Haematology and Immunohematology • Microbiology and Infectious Disease Serology • Histopathology • Cytopathology
Medical Imaging-Conformity Assessment Bodies	• Projectional Radiography: X-Ray, Bone Densitometry (DEXA), Dental X-Ray-OPG • Fluoroscopy • Computed Tomography (CT) • Magnetic Resonance Imaging (MRI) • Ultrasound • Colour Doppler
Proficiency Testing Providers (PTP)	• Testing • Calibration • Medical • Inspection
Reference Material Producers (RMP)	• Chemical Composition • Biological and Clinical Properties • Physical Properties • Engineering Properties • Miscellaneous Properties

(Source: www.nabl-india.org/about-nabl/accreditation-schemes/)

4.9.6 Advantages of NABL

NABL accreditation has many advantages for the organizations, PTPs and RMPs. Some of them are:

1. Increases credibility of the testing reports (issued by the specific lab).
2. Building up of confidence for the organization in calibrating and testing the reports.
3. Accreditation ensures the quality assurance systems of the organization.
4. Customers' satisfaction.
5. Customers of these accredited organizations/ laboratories can have greater access for their products, in both domestic and international markets.
6. Market acceptability and increased potential in business.
7. Elimination of need of re-testing.
8. Monitoring of maintenance of efficacy for long time.

9. Improvement in the process.
10. Employee's/Staff's education and training can be overlooked.
11. Increases market opportunity for RMPs.
12. The accreditation assures the quality control methods, validation methods, quality assurance, calibrations for the RM (reference materials), so, the use of CRM (certified reference materials) build the confidence for the RMPs and also the re-checking of CRM can be eliminated.

4.10 GLP (GOOD LABORATORY PRACTICE)

4.10.1 Introduction

GLP was introduced for the non-clinical safety studies in 1976. In late 90's this practice along with OECD (Organization for Economic Co-operation and Development) was accepted as industry standards. GLP has been introduced due to the poor and dishonest practice in laboratory in the early 70's. The poor lab practices include wrong calibration of equipments, inaccurate test systems and accounts. In 1983, Industrial Bio Test Laboratory (1952-1978) of New York was found guilty as it provided wrong and inaccurate research data to the Government. The company provided fake, fabricated and concealed data of the tests on rodents involving Trichlorobanilide (deodorant soap additives), Naprosyn (arthritis drug), Sencor (Herbicide) and Nemacur (Pesticide).

4.10.2 Definition

According to Valcarcel M., GLP is a set of rules, operating procedures and practices established by an organization to ensure the quality and accurate results in a laboratory practice. In this practice, the given organization sets the principles and the laboratory works are planned, operated, overlooked and reported.

4.10.3 Fundamentals of GLP

4.10.3.1 Resources

It includes the following:

1. **Organization and Management:** Management has the overall responsibility for the implementation of both good science and good organization within their institutions. Good science includes proper definition of experimental design, knowledge of scientific principles, documentation of experimental and environmental variables, complete evaluation of the results and reporting of results. Whereas, good organization should provide proper planning of studies, qualified skilled personnel, adequate facilities, infrastructures, proper conduction of studies and verification process for the study results.
2. **Personnel:** The detailed records should be maintained for every individual staff of the institution. The records include the detail curriculum vitae, training records and their job descriptions. These records should meet the GLP requirements and these

are maintained to establish that every staff has the competence, education, experience and training to perform the tests.

3. **Availability of Facilities:** Adequate facilities with state-of-the-art infrastructure should be provided by the institution and management to ensure the validation of the studies. The cleaning, maintenance and documents of the site plan should satisfy the guidelines.
4. **Availability of Equipments:** Adequate equipments must be available for the study in the organization. The suitability of the equipment and calibrated instruments should be provided by the management.

4.10.3.2 Characterization

It includes:

1. **Test Items:** It may be an active ingredient for a medicine, a pesticide, a food additive, a vaccine, an industrially used chemical, a biomass or an extraction from plants. These items are characterized by analytical profile like chemical identification test, solubility, stability etc. The test items should be stored properly to avoid the contamination.
2. **Test Systems:** The test systems could be the animals, bacteria, cells, organs and plants. Sometimes they may be analytical equipments also. The test systems should be handled in such a way that it must comply with the GLP guidelines and with the national animal welfare law.

4.10.3.3 Rules

1. **Study Protocols:** The study plan or protocol describes how the study is designed and how it is to be conducted. The plan should include the expected timeframe of the study.
2. **Written Procedures:** Written procedures are often known as SOPs (Standard Operating Procedures). SOPs provide the instructions how each technical procedure should be performed, how to ensure the sound organization of the study, environmental variables and data.

4.10.3.4 Results

It includes raw data, final reports and data archiving.

1. **Raw Data:** The original record and the data needed for the reconstruction should be recorded. The raw data should include '*what*' was done, '*how*' it was done, '*when*' the work was done and '*who*' performed the work. The recorded data should clarify the process by which it is generated and should confirm the process has been performed as per the guidelines and SOPs.
2. **Final Results:** Final results are the responsibility of the study director. These results should describe the study accurately and the scientific interpretation. The results

should reflect accurately the raw data. The review and audit of these reports should be done. All accepted changes in the results approved by the reviewer should be incorporated before the finalization of the results.

3. **Archives:** Archiving is a safe depositing of all information. It is considered to be a center for the compilation and distribution of summary documents. The archiving of document helps the reconstruction of studies performed earlier.

4.10.3.5 Quality Assurance

The requirement of the quality assurance is to validate the experimental results. Quality assurance unit (QAU) or simply QA must review all phases of preclinical research, organization framework, staff documents, study procedures and SOPs. The internal audits and inspections should be performed by the QA officers. The QA performs the study-based audit, facility and systems-based inspection and process-based inspections.

4.10.4 GLP Principles

GLP principles are set of organizational requirements. GLP is a regulation covering the quality management of non-clinical safety studies. The aim of the regulation is to encourage scientists to organize and perform their studies in a way which promotes the quality and validity of the test data. GLP deals with the following issues:

- The facility provided by the organization.
- Efficient and trained personnel.
- Quality of validated equipment and reagents.
- Predetermined study design.
- SOPs, process validation and test procedures.
- Correctness of the results.
- Quality assurance laboratory (QAL) and Quality assurance program (QAP).
- Recorded and documented results and their storage.

The organizations should fulfill all the criteria to provide all the facilities for the good practice in laboratory. The personnel should have enough knowledge about the principles and working of the practices. In the elements of GLP, SOP is an important part with respect to quality assurance. To maintain the productivity of the result, a well documented SOP is required; moreover, the personnel should have complete information mentioned in SOPs. SOPs define the complete process flow and work steps which help to achieve the accurate and precised results. Validated modern equipments and adequate facilities should be provided by the organization to maintain the good practice in laboratory. The complete specifications and storage of reagents and materials should be provided. QA laboratory should have the proper test procedures (physical, chemical and biological) and characterized data for both the test and reference materials. Quality assurance unit (QAU) bears the responsibility to assure the GLP and this unit is attached with QAL and QAP. The audit of the

laboratory and verification of the quality parameters are the major responsibilities of the QAU. The reported study results should be stored and retained with well documented manner.

4.10.5 Aim of GLP

1. GLP helps to reduce the number of false negatives arising from the studies. False negative result for a toxicity study falsely intimated that the test item is not toxic, but in real the item is toxic.
2. GLP also helps to reduce the chance of false positives. In the case of a non-clinical safety study, the results wrongly predict that the test item is toxic, when really it is not.
3. GLP promotes international recognition of study data. When studies are performed according to OECD GLP principles, then the acceptability and reliability of the data are recognized in the international level by the OECD member states.

QUESTIONS

Multiple Choice Questions

1. Quality management system deals with ……
   (a) Quality for their products and services
   (b) Safety for their products and services
   (c) Quality and safety for their products
   (d) Quality and safety for their products and services
2. Quality control is defined as ……
   (a) Sampling and documentation
   (b) Sampling, specification and documentation
   (c) Sampling, specification, testing, documentation and release procedures
   (d) None of these
3. ICH guidelines involve ……
   (a) Quality, Safety
   (b) Quality, Safety and Efficiency
   (c) Quality control and Multidisciplinary guidelines
   (d) Quality, Safety, Efficiency and Multidisciplinary guidelines
4. Carcinogenicity and Genotoxicity study is a …… aspect of ICH guidelines.
   (a) Safety guidelines (b) Efficiency guidelines
   (c) QSEM guidelines (d) All of these
5. Pharmacovigilance is a part of ……
   (a) ICH E1 guidelines (b) ICH E3 guidelines
   (c) ICH E2 guidelines (d) ICH E2 (A-F) guidelines

6. Key components of TQM are ……
   (a) Consumer/Customer focus (b) Continuous improvement
   (c) Involvement of employee (d) All of these
7. Six sigma concept includes …….
   (a) Define, Measure, Analyze, Improve and Control
   (b) Design, Measure, Analyze, Improve and Control
   (c) Define, Manage, Analyze, Improve and Control
   (d) All of these
8. The basic principle of ISO 9000 is ……
   (a) Customer focus and Engagement of people
   (b) Relationship management and Leadership
   (c) Evidence based decision making and Continuous improvement
   (d) All of these
9. ISO 14000 relies on ……
   (a) DMAIC model (b) PDCA model
   (c) Six-sigma concept (d) All of these
10. Guidelines for Environmental performance evaluation is included in ……
   (a) ISO 14004 (b) ISO 14001
   (c) ISO 14040 (d) ISO 14031

ANSWERS

1. (d)	2. (c)	3. (d)	4. (a)	5. (d)	6. (d)	7. (a)	8. (d)	9. (b)	10. (d)

Long-Answer Questions:

1. Write a note on ICH guidelines.
2. Explain the principles of TQM and QBD.
3. Write about the six sigma concepts.
4. Define OOS. How will you find out the possible OOS in the results? Explain.
5. Write the basic principles of ISO 9000. Explain ISO 9000 series in detail. Write a note on requirements of ISO 9000 Series.
6. What is EMS? Write the basic working principle of ISO 14000 series. What are the advantages of it?
7. Write a short note on GLP and NABL.

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Chapter ... 5

INDIAN REGULATORY REQUIREMENTS

♦ LEARNING OBJECTIVES ♦

After completing this chapter, students will be able to understand:

- The Central Drug Standard Control Organization is licensing authority (regulatory agency) for the approval of new drugs proposed and amount of drugs to be imported.
- Developing standard and regulatory measures for drugs linguistics and devices.
- Laying down regulatory measure by amending acts and rules.
- Regulating the market authorization of new drugs.

  In its role on the regulator of imported drugs, the CDSCO works with:
- The Drugs Technical Advisory Board and Drugs Consultative Committee.
- The Central Drugs Laboratory undertaken testing of such drugs.

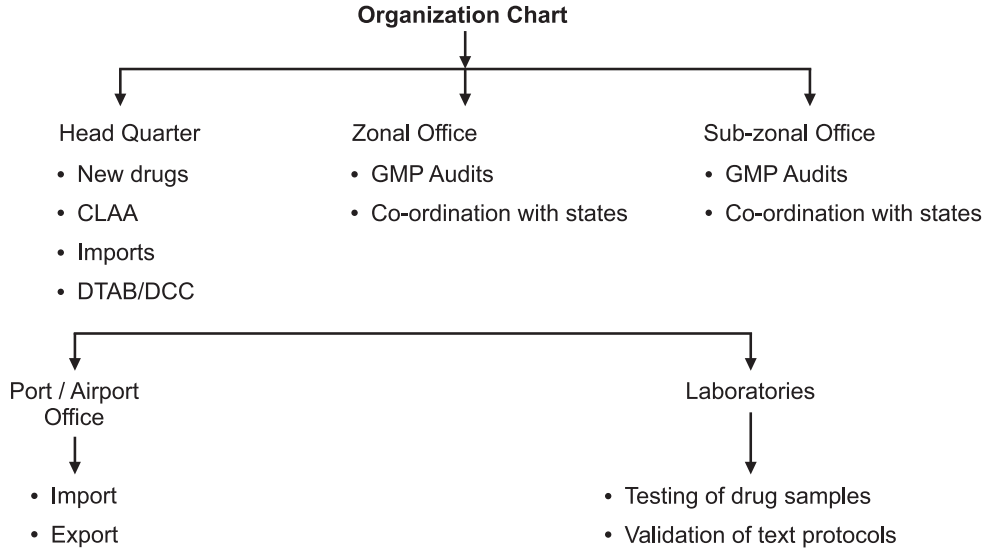
5.1 INTRODUCTION

The Central Drug Standard Control Organization (CDSCO) regulates drugs, cosmetics, diagnostics and devices in India. It is headed by the Drug Controller General of India (DCGI), responsible for safety, efficiency and quality standards for pharmaceuticals and medical device and publisher of the Indian Pharmacopoeia. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Commission (DCC). State Government is responsible for licensing, approvals, inspection and recalls of drugs manufactured within their domain. India is main regulatory body for regulation of pharmaceuticals and medical devices and the Drug Controller General of India (DCGI) is responsible for the regulation of pharmaceuticals and medical devices. The CDSCO works with the World Health Organization to promote Good Manufacturing Practice (GMP) and international regulatory harmony. The organization responsible for approved issuance of license for various categories of drugs such as blood and blood products, I.V. fluids, vaccines, sera etc., either manufacturing in India or imported. It regulates the manufacturing, sale, distribution of drugs through the state authorize and register manufacturing, sale and distribution of drugs.

5.2 CENTRAL DRUG STANDARD CONTROL ORGANIZATION (CDSCO)

The CDSCO is the main regulatory body for regulation of pharmaceuticals, medical devices and clinical trials. The head office of CDSCO is located in New Delhi and it is functioning under the Control of Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India.

Drug Controller General of India (DCGI): He/She is responsible for approval of new drugs, medical devices and clinical Trials to be conducted in India. The person who is appointed by the Central Government under the DCGI the state drug control organization will be functioning. The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC).



Zonal Office: Mumbai, Kolkata, Chennai, Ghaziabad, Ahmadabad, Hyderabad.

These centers are involved in GMP audits and inspection of manufacturing units of large volume, parental, sera, vaccine and blood products.

Sub-zonal Office: Chandigarh, Jammu, Bangalore.

These centers are coordinated with state drug control authorities under their jurisdiction for uniform standard of inspection and enforcement.

❖ **Central Drugs Testing Laboratories:**

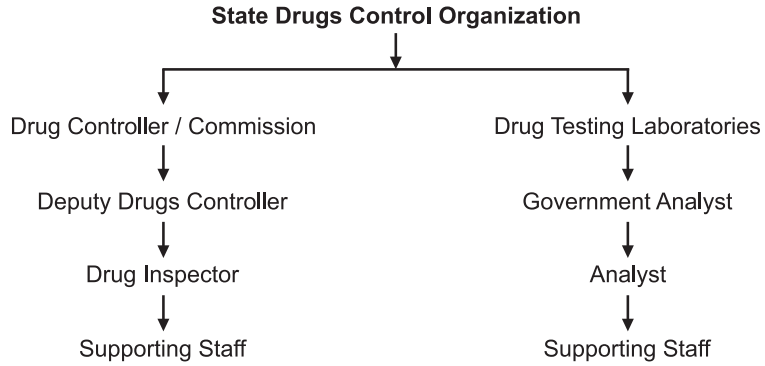
1. Central Drugs Laboratory, Kolkata.
2. Central Drugs Testing Laboratory, Mumbai.
3. Central Drugs Testing Laboratory, Chennai.
4. Central Drugs Laboratory, Kasauli.
5. Regional Drugs Testing Laboratory, Guwahati.
6. Regional Drugs Testing Laboratory, Chandigarh.

These laboratories are responsible for quality control of Drugs and Cosmetics in India.

❖ **Functions of CDSCO:**

1. Approval of new drugs and clinical trials.
2. Import Registration and Licensing.
3. Licensing of Blood banks, LVPS, Vaccines, Pie-DNA products and some medical devices and diagnostic agents.
4. Amendment to D and C Act and Rules.
5. Banning of drugs and cosmetics.
6. Grant to Test license, Personal License, NOC'S for export.
7. Testing of drugs by Central Labs.
8. Publication of Indian Pharmacopoeia.
9. Monitoring adverse drug reactions.
10. Guidance on technical matter.

5.3 STATE DRUGS CONTROL ORGANIZATION



❖ **Functions of State Licensing Authorities**:

1. Licensing of drug testing laboratories.
2. Approval of drug formulation for manufacture.
3. Monitoring of quality of Drugs and Cosmetics, manufactured by respective state and those marketed in the state.
4. Investigation and prosecution in respect of contravention of legal provision.
5. Administrative actions.
6. Pre and post licensing inspection.
7. Recall of substandard drugs.

5.4 APPROVAL OF NEW DRUG

1. The drug approval process varies from one country to another.
2. In some countries, only a single body regulates the drugs and it is responsible for all regulatory tasks such as approval of new drugs.

3. New drug will not be imported, except under permission granted by the Licensing Authority, accomplished by fifty thousand rupees.
4. The licensing authority, after being satisfied that the drug if permitted to be imported as raw material (bulk drug substance) or a finished permutation will be effective and safe for use in the country may issue import permission.
5. For new drug discovered in other countries, phase-I trials are not usually allowed to be initiated in India.

❖ **Approval for Clinical Trials:**

1. Approval for clinical trials and application to conduct clinical trials in India should be submitted along with the date of chemistry, manufacturing, control and animal studies to DCGI.
2. The data regarding the trail protocol investigators brochures and informed consent documents should also be attached.
3. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only the after approval of DCGI and ethical committee.

❖ **Approval of Clinical trials, Import and Manufacture of New Drugs:**

Requirements and Guidelines:

Schedule Y

Rule 122A – Permission to import new drug.

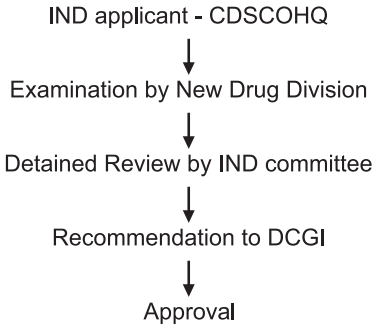
Rule 112B – Permission to manufacture new drug.

Rule 122DA – Definition of clinical trials.

Rule 122E – Definition of new Drugs.

1. New substance having therapeutic indication.
2. Modified on new claims, new route of administration for already approved drug.
3. Fixed dose combination.

❖ **Approval of IND:**



Time Line:

Phase-I: 90 days

Phase-II: 45 days

Phase-III: 60 days

❖ **Import, Registration and Licensing:**

Manufacturing sites and products are required to be registered.

Issue of import license in form 10/10 A.

Rules 21 to 30: Rules related to grant of registration certificate and import license.

Schedule DI and DII: Information required for registration of manufacturing site and product.

Time line for RC: As per D and C rules, 9 months; however in practice, 2 months.

For import license 2-3 weeks.

As per Rules 21A (5), there is provision to import manufacturing site for which manufacture has to pay 5000 USD.

5.5 REQUIREMENTS FOR IMPORT AND REGISTRATION

❖ **Registration of Overseas Manufacturing Site and Drugs:**

Registration certificate is issued in form 41 by licensing authorities. Import license issued in form 10 and 10 A.

Central Licensing

CLAA approval and grant of license.

Manufacture

↓

State licensing Authorities (license prepared by state licensing authority).

↓

Joint Inspective by State and Central Inspectors.

Examination of Report

↓

For biological, Large volume parenterals (LVP), Blood Bank and blood products and some medical devices.

❖ **Global Clinical Trials:**

Permission is required from CDSCO for conducting global clinical trials in the country.

Phase-I for new drugs substance is developed outside India, whereas inside is not permitted.

5.6 CENTRAL DRUGS TESTING LABORATORY (CDTL)

1. Central Drugs Testing Laboratory (CDTL), Kolkata:

The Central Drugs Testing Laboratory, Kolkata is the national statutory laboratory of the Government of India for quality control of drugs and cosmetics, and is established under the Indian Drugs and Cosmetics Act, 1940. It is the oldest quality control laboratory of the drug control authorities in India. It functions under the administrative control of the director general of health services in the ministry of health and family welfare.

The major functions of the laboratory include:

Statutory Functions:

1. Analytical quality control of majority of the imported drugs available in Indian market.
2. Analytical quality control of drugs and cosmetics manufactured within the country and behalf of the central and state drug controller administration.
3. Acting an appellate authority in matters of disputes relating to quality of drug.

Other Functions:

1. Collection, storage and distribution of international standard international reference, preparation of drugs and pharmaceutical substances.
2. Preparation of national reference standard and maintenance of such standard. Maintenance of microbial cultures is useful in drug analysis distribution of standard and cultures to state quality control laboratories and drug manufacturing establishment.
3. Training of drug analysts deputed by state drug control laboratories and other institutions.
4. Training of World Health Organization follows from abound or modern method of drug analysis.
5. To advice the central drug controls administration in respect of quality and toxicity of drugs awaiting license.
6. To work out analytical specification for preparation of monographs for the Indian Pharmacopoeia and the Homeopathy Pharmacopoeia of India.
7. To undertake analytical research on standardization and methodology of drugs and cosmetics.
8. Analysis of Cosmetics received a survey samples from central drug standard control organization.
9. Quick analysis of life saving drug on an all India basis received under national survey of quality of essential Drug Program from zonal offices of Central Drug Standard Control Organization.

2. Central Drugs Testing Laboratory (CDTL), Chennai:

Central Drugs Testing Laboratory, Chennai is one of the national laboratory in India engaged in the research and analysis of drugs and cosmetics as per Drugs and Cosmetics Act, 1940.

3. Central Drugs Testing Laboratory (CDTL), Mumbai:

The Central Drugs Testing Laboratory, Mumbai is another national statuary laboratory of Government of India, functioning under administrative control of the Drug Controller General (India), DGHS Ministry of Health and Family Welfare.

The major functions of the laboratory include:

Testing of imported bulk drugs and formulations: The Laboratory is notified as appellate laboratory for copper T intra-uterine. Contraceptive device and tubal rings under the drug and cosmetic rules, (Medical stores) and regional directors of department of family welfare and procurement and field samples of oral contraceptive pills, copper T and tubal rings referred by the department of family welfare.

4. Regional Drugs Testing Laboratory (RDTL), Guwahati:

The Regional Drugs Testing Laboratory, Guwahati is the one of the five National Laboratories of the Government of India for quality control of Drugs and Cosmetics and was established under the Indian Drugs and Cosmetics Act, 1940 functioning under administrative control of the Drugs Controller General of India and sub-ordinate office under Directorate General of Health Services, Ministry of Health and Family Welfare. The laboratory was set up in the year 2002 for entire North Eastern States including Sikkim and is housed in its own building at Guwahati.

❖ **Statutory Functions of Laboratory include:**

1. Analytical quality control of Drugs and Cosmetics manufactured within the country on behalf of the Central and State Drugs Controller Administration.
2. To assist the Central Drugs Standard Control Organization in the testing of drugs and cosmetics.

5. Regional Drugs Testing Laboratory (RDTL), Chandigarh:

The Regional Drugs Testing Laboratory (RDTL), Chandigarh has become operational since November 2007. Presently the laboratory is testing the drugs at an average of 50 samples per month, primarily to cater the requirement of CDSCO (North-Zone) The laboratory is in the process of upgradation in infrastructure of CDSCO (North-Zone). The laboratory is in the process of upgradation in infrastructure and manpower in order to increase the testing capacity.

❖ **Functions undertaken by the Central Government:**

Statutory Functions:

1. Laying down standards of drugs, cosmetics, diagnostics and devices.
2. Laying down regulatory measures, amendments to Acts and Rules.
3. To regulate market authorization of new drugs.
4. To regulate clinical research in India.
5. To approve licenses to manufacture certain categories of drugs as Central License approving authority i.e. for blood banks, large volume parenterals and vaccines and sera.
6. To regulate the standards of imported drugs.
7. Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC).
8. Testing of drugs by Central Drugs Labs.
9. Publication of Indian Pharmacopoeia.

Other Functions:

1. Co-ordinating the activities of the State Drugs Control Organization to achieve uniform administration of the Act and Policy Guidance.
2. Guidance of technical matter.
3. Participation in the WHO GHP certification scheme.
4. Monitoring training program for regulatory official and Government Analysts.
5. Conducting training program for regulatory official and Government Analysts.
6. Distribution of quotes of Narcotic drugs for use in medicinal formulations.

❖ **Functions Undertaken by State Government:**

1. Licensing of drug manufacturing and sales establishments.
2. Licensing of drug testing laboratories.
3. Approval of drug formulations for manufacture.

5.7 CERTIFICATE OF PHARMACEUTICAL PRODUCT (COPP)

The certificate of pharmaceutical product is a certificate issued in the format recommended by the World Health Organization (WHO), which establishes the status of the pharmaceutical product and of the applicant for this certificate in the exporting country. It is issued for a single product, because manufacturing arrangements and approved information for different pharmaceutical forms and strengths can vary.

Importance:

1. It is needed by the importing country when the product in question is infected for Registration (Licensing and Authorization) or renewal of registration.
2. With the scope of commercialization or distribution in that country.
3. Certification has been recommended by WHO to help undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities in importing countries to assess the quality of pharmaceutical products as prerequisite of registration or importation.

Scope:

The Certificate of a Pharmaceutical Product is needed by the importing country when the product in question is intended for registration (licensing, authorization) or renewal (prolongation) of registration, with the scope of commercialization or distribution in that country. Certification has been recommended by WHO to help undersized drug regulatory authorities or drug regulatory authorities without proper quality assurance facilities in importing countries to assess the quality of pharmaceutical products as prerequisite of registration or importation. In the presence of such COPP, WHO recommends the national authorities to ensure that analytical methods can be confirmed by the national laboratory, to review and if necessary to adapt the product information as per local labeling requirements, and to assess bioequivalence and stability data if necessary. However, regulatory practices often vary in importing countries. Thus, in addition to CPP, assessment of application dossiers to support drug registrations, with different levels and complexity of requirements are considered necessary to satisfy full assurance on the appropriate quality of drugs.

WHO: The application for grant of WHO GMP Certificate of Pharmaceutical Product should be made to respective zonal/sub-zonal officers as per the requirement. The COPP should be issued by zonal/sub-zonal officers on behalf of Drugs Controller General (India) after inspection and satisfactory clearance by CDSCO officers as per WHO-GMP guidelines.

General Requirements for Submission of Application for Issue of COPP:

A forwarding letter/application should be addressed to DDC (I) / ADC (I) of respective CDSCO zonal/sub-zonal offices with copy of covering letter and product summary sheet to DCG (I) by authorized person only.

1. Application should clearly indicate for fresh certification (Grant) or reissue of products applied, accordingly it will be scrutinized for the products applied.
2. Applications should be reviewed by CDSCO officers and completed applications in all respects should be accepted for inspection on first come first serve basis.
3. The forwarding letter/application shall be accompanied with list of products applied for grant of COPP, along with a product permission copy (manufacturing license issued by the SLA) and notarized product summary sheet, site master file as per WHO-GMP requirement.

List of major/master documents like master validation plan, quality manuals, specifications, master formula records maintained by firm and list of SOPs (to indicate the documentation system of firm).

Manufacturing Layout:

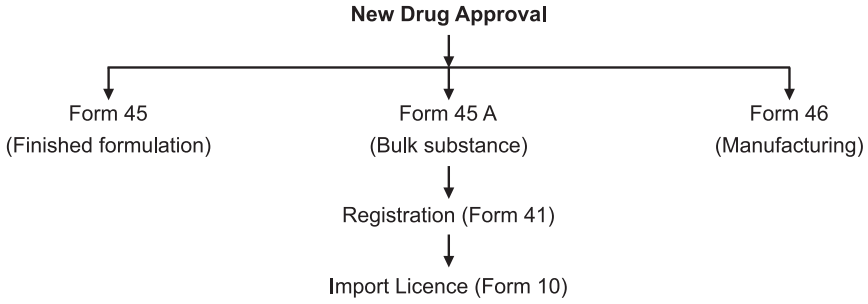
1. List of personnel (with designation, qualification and experience), List of equipments, instruments, utilities along with make and model and capacity.
2. List of primary and secondary impurity and reference standards/cultures available with the firm (relevant to the applied products for grant of COPP).

Procedure for Accepting the Application for Issue of COPP:

The certificate of pharmaceutical product has been issued under WHO-GMP based on guidelines laid down by health agency and also aimed at diminishing the risk inherent in pharmaceutical productions. The certificate helps the regulator to ensure that drugs are consistently produced and are quality controlled before they leave the country.

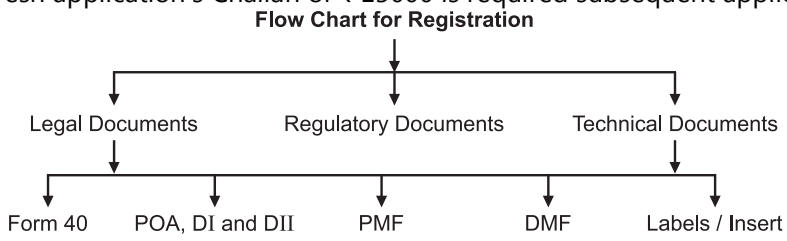
Documents Required for Applying for Grating or Revalidation of COPPs:

1. Application from manufacturer.
2. Site master file (as specified under WHO TRS 823).
3. Cost of manufacturing license.
4. List of approval products.
5. List of products applied for issuance of COPPs.
6. List of SOPs and STPs.
7. Stability data (3 batches) accelerated/Real time.
8. List of equipments and instruments.
9. List of technical staff, their qualification, and experience and approval status.
10. Manufacturing layout plan.
11. Process validation for 3 batches of each product.
12. Schematic diagram of water system specifying circulation loop and MOC (Material of construction).
13. Schematic diagram of HVAC system specifying terminal filter configuration.
14. Export data of last 2 years in case of revalidation.
15. Product money sheet.



Time Line and Fees for NDA:

It generally takes about one year to secretaries these documents by technical data associates/Drug inspector of CDSCO during the period clarification if any, are required by them are answered and there after the imported gets the approved TR Challan of ₹ 50000 is required for fresh application's Challan of ₹ 15000 is required subsequent application.



Legal Documents:

1. Documents to be submitted by Indian agent.
2. **Form 40:** It should be signed and stamped by Indian agent.
3. Documents to be submitted by manufacturer.
4. **POA:** Power of attorney should be consulate from Indian embassy of the other country of origin, and should be co-jointly signed by both the parties i.e. manufacturer and Indian agent.

Schedule DI and DII:

They should be signed and stamped by manufacturer (Need not to be notarized).

Regulatory Documents:

1. Notarized plant registration certificate.
2. Notarized manufacturing and marketing license
3. Notarized free sale certificate
4. GMP/COPP certificate notarized.

Technical Documents:

(A) Plant master file: It should include the following points:

- Sketch of the plant.
- Profile of the company.
- Organogram of the company.
- Plant and machinery.
- Hygienic and sanitary measure details.
- IQPQDQOQ.
- HAVAC system.
- Men material movement.

(B) Drug master file: It should include the following points:

- Manufacturing process/flow chart.
- Quality assurance procedures/process controls.
- The provision to control contamination and cross contamination in the final product.
- Process control, control of critical steps and intermediates.
- Container closure system.
- Risk Assessment as per ISO 14971.
- Process validation/verification.
- Stability data.
- Biocompatibility and toxicological data.
- Clinical studies and reports.

Post marketing Surveillance: It is the part of Device Master File, and it should include following points:

- Procedures for distribution of records.
- Complaint handling.
- Adverse incident reporting.
- Procedure for product recall.
- Corrective action taken.

(C) Labels and Inserts:

Product labels should show the address of manufacturer. Product inserts should describe the brief description of the product and its intended use.

Processing Procedure: After ensuring all documents correctly as per the requirements of FDA, it generally takes about 2-3 months to scrutinize these documents by Technical Data Associates/Drug inspectors of CDSCO and during this period, clarifications if any, required by them are answered and thereafter we get the Registration Certificate (RC) in Form 41.

Import Processing: After getting the registration certificate from CDSCO, the Indian agent is to import the products from the manufacturer. Following documents are further required to get Form 10 (Import license).

Form 8: TR Challan - (₹ 1000 for 1st product then ₹ 100 for each additional product).

Form 9:

- ❖ Copy of Wholesale License (Indian agent)-Notarized.
- ❖ Copy of Registration Certificate-Notarized.

Time Line For Import License: The Importer (Indian agent) is not authorized to import the products from foreign manufacturer unless he obtains Import license (Form 10) from CDSCO. It generally takes about one month to scrutinize these documents by Technical Data Associates/Drug inspectors of CDSCO and during this period, clarifications if any, required by them, are answered after that the importer gets the Import license. For Import license application TR Challan of ₹ 1000 for 1st product then ₹ 100 for each additional product is required.

QUESTIONS

Multiple Choice Questions:

1. Approximately what percentage of clinical development studies are conducted by CRO's?
   (a) 1-5% (b) 10-20%
   (c) 25-30% (d) 50-75%
2. What is the approximate ratio of potential compounds from the beginning of Development to number of products that ultimately get FDA approval?
   (a) 1 : 10 (b) 1 : 100
   (c) 1 : 1,000 (d) 1 : 10,000
3. On which two criteria does the FDA classify NDAs?
   (a) Novelty of the active ingredient and time to market
   (b) Balance between safety and effectiveness
   (c) Novelty of the active ingredient and clinical improvement
   (d) Clinical improvement and effectiveness of product
4. What is a synonym/description for the Phase 4 trials?
   (a) Post Marketing Surveillance (b) Pre Marketing Surveillance
   (c) Pre FDA Approval (d) Post FDA Approval
5. What is the purpose of pre-clinical testing?
   (a) To verify that a drug is sufficiently safe and effective to be tested in humans.
   (b) To create a basic outline for the larger scale future tests on a widespread population.
   (c) To undergo preliminary testing in healthy humans to monitor the effects of the drug.
   (d) None of above

ANSWERS

1. (c)	2. (c)	3. (a)	4. (a)	5. (a)

Long-Answer Questions:

1. Explain the details of CDSCO and give its functions.
2. Write about various Drug Regulatory agencies.
3. Write details about different Central Drugs Testing Laboratories available in India.
4. Write short note on State Licensing authorities.
5. Explain about Central Drugs Laboratory and its function.
6. What is RDTL and its function?
7. What is COPP and its importance?
8. What are general requirements for submission of application for issue of COPP?
9. What is the procedure for accepting the application for issue of COPP?
10. What are the documents required for applying grating on revalidation of COPP?
11. What are the regulatory requirements and approval procedures for new drugs?

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